TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD

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DECLARATION

I declare that the thesis entitled **"TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD"** has been prepared by me under the guidance of **Dr. Varun Mehta**, Professor, Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated
To My Respected
Teachers, Family
& Friends

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Dr. Gaurav Maurya

LIST OF ABBREVIATIONS

ALP	Alkaline Phosphatase
BMI	Body Mass Index
CAP	Controlled Attenuation Parameter
DM	Diabetes Mellitus
HDL	High Density Lipoprotein
HTN	Hypertension
IR	Insulin Resistance
kPa	Kilo Pascal
LDL	Low Density Lipoprotein
LSM	Liver Stiffness Measurement
MR	Magnetic Resonance
MS	Metabolic Syndrome
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steatohepatitis
TE	Transient Elastography
TGs	Triglycerides
USG	Ultrasonography

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is commonly diagnosed in obese or overweight individuals. However, non-obese individuals with NAFLD are not rare but represent one significant end of the phenotypic spectrum of NAFLD. Many aspects of non-obese NAFLD need further exploration including epidemiology. This study was done to estimate the frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

Aim of Study: To determine frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

Materials & Methods: All non-obese NAFLD patients of age more than 18 years (determined by BMI</=22.9kg/m2) attending the OPD and admitted in gastroenterology department of DMCH within 1 year (march,2018 to march,2019) were enrolled in this study. Diagnosis of fatty liver was done by ultrasonography. All subjects underwent fibroscan to determine degree of fibrosis. Total number of patients enrolled were 121.

Results: Age of patients ranged from 30 to 63 years. Maximum number of patients were aged between 41-50 years (51.2%). 61.2% patients were males and 38.8% were females. 36.4% patients were hypertensive and 39.7% were diabetic. 52.9 % patients had hypertriglyceridemia and 56.2 % patient had dyslipidemia. Frequency of fibrosis in our study of non-obese NAFLD was 20.7 % (25/121). 14% patients had mild fibrosis, 5% had moderate and 1.7% had significant fibrosis. Mean kPa value was 5.2+/-0.79 in our study. 80% of patients with fibrosis in our study were diabetic. 84% of patients with fibrosis had hypertriglyceridemia. There was a direct and significant association between diabetes and hypertriglyceridemia with presence and severity of fibrosis (p value<0.05)

Conclusion: In conclusion, frequency of fibrosis in non-obese NAFLD patients in our study was 20.7%, with significant fibrosis (>/=F3) seen in 1.7%. Statistically significant association between diabetic status and abnormal lipid profile with presence and severity of fibrosis in non-obese NAFLD patients was established in our study.

Keywords: Fibroscan, non-obese, NAFLD- non-alcoholic fatty liver disease, fibrosis.

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INTRODUCTION

In today's world liver diseases play an increasingly important role. The most common liver disease is non-alcoholic fatty liver disease (NAFLD)[1,2]. It is a major cause of chronic liver disease. Nonalcoholic fatty liver disease (NAFLD) refers to a group of conditions characterized by hepatic steatosis in the absence of significant alcohol consumption. An exact number cannot be determined because NAFLD is an asymptomatic disease and patients with NAFLD can therefore go undetected[3].

NALFD encompasses a spectrum of clinical-histological phenotypes from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) which can progress to cirrhosis[4]. The spectrum of NAFLD ranges from simple steatosis (hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or fibrosis) and non-alcoholic steatohepatitis - NASH (defined as the presence of hepatic steatosis and inflammation with hepatocellular injury or ballooning with or without fibrosis) to cryptogenic cirrhosis. Non-alcoholic fatty liver disease (NAFLD) is fast attaining the status of being the most common liver disease throughout the world. Its prevalence is as high as 20-30% of general population in western countries[5-8]. In India, its prevalence in general population ranges from 9 to 32% in different studies[9-11].

NAFLD is seen commonly in patients with metabolic abnormalities associated with obesity such as type II diabetes, dyslipidaemia, and metabolic syndrome[12,13]. Obesity is considered a key player in the development of NAFLD and the majority of patients with NAFLD are either obese or overweight. Evidently however not all obese subjects develop NAFLD.

Although non alcoholic fatty liver disease (NAFLD) is usually associated with obesity, patients who are not obese can also present with NAFLD. This subset of individuals known to have ‘lean NAFLD’ or ‘non-obese NAFLD’ is becoming increasingly prevalent. NAFLD in lean patients appears to be more common among Asians. Risk factors for

NAFLD in lean patients include high body fat, body weight gain even within normal weight limits, high fructose and high cholesterol intake, and genetic risk factors[14].

NAFLD occurring in nonobese subjects has been reported in children and adults residing in developing countries as well as developed countries. It appears to be recognized more frequently in Asians, even when strict ethnicity specific body mass index criteria are used to define obesity[15-21]. Non-obese NAFLD may represent a distinct entity rather than merely a by-product of different body mass index (BMI). Moreover, NAFLD in the non-obese subjects suggests a phenotypic distinctiveness that raises the possibility of a different pathophysiology.

Although NAFLD in lean individuals is generally considered a less severe form of liver disease than NAFLD in obese patients, this conception has recently been challenged.

NAFLD is assuming higher importance now because of:

1. The possible role in the development of cardiovascular disease.
2. The association with diabetes and impaired glucose tolerance.
3. The strong relationship with metabolic syndrome.

Early diagnosis and management of NAFLD is thus of vital importance[22].

Dietary modification and exercise constitute the mainstay of treatment. As the link to non communicable diseases is clear, there is a need to address this as a public health problem.

Recent multinational investigations reveal an increased mortality in non-obese individuals with NASH and NAFLD. Many aspects of lean NAFLD need further exploration including epidemiology and prevalence of fibrosis.

Ultrasound detects fatty liver with a good sensitivity but does not differentiate simple steatosis from steatohepatitis. Serum transaminases have low value in predicting steatohepatitis. The only gold standard test for detection of this fraction with increased risk of progression is liver biopsy. However, application of liver biopsy to all patients with NAFLD is impractical.

Various studies have proved that Fibroscan has high accuracy in detecting level of fibrosis in NAFLD and can be a good alternative for liver biopsy in patients who cannot undergo invasive procedures. Fibroscan is an easy and non-invasive method to evaluate liver fibrosis, needing short time to obtain results[23].

There is limited information regarding prevalence of fibrosis in non-obese individuals of NAFLD using Fibroscan in India, hence this study was planned.

AIMS AND OBJECTIVE

2.1 PRIMARY OUTCOME:

To determine frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

2.2 SECONDARY OUTCOME:

Correlation of fibrosis in non-obese individuals of NAFLD with age, diabetes and hypertriglyceridemia.

REVIEW OF LITERATURE

Nonalcoholic fatty liver disease (NAFLD) is a broader term with a spectrum including patients with simple steatosis, steatohepatitis that can progress to cirrhosis liver and even hepatocellular carcinoma[24,25]. In 1980, Ludwig et al[26] described the term NASH as a form of liver injury that was histologically consistent with alcoholic hepatitis but occurred in obese, diabetic females who denied alcohol use. The prevalence of NAFLD and NASH in the general population is estimated to be between 10%-24% and between 1%- 5% respectively. In India prevalence of NAFLD is around 9% to 32% of general population[9,11]. Nonalcoholic fatty liver disease (NAFLD) is a common clinicopathological condition characterized by significant lipid deposition in the hepatocytes of the liver parenchyma. The pathological picture bears a striking resemblance to that of alcohol-induced liver injury but it occurs in individuals who deny a significant history of alcohol ingestion. NAFLD comprises a wide spectrum of liver damage ranging from simple macro vesicular steatosis to steatohepatitis, advanced fibrosis, and cirrhosis[27]. Subsets of NAFLD which progress to cirrhosis are being increasingly recognized as a major cause of liver-related morbidity and mortality with the potential to progress to liver failure. Before diagnostic tests for hepatitis C were available cases of NAFLD were diagnosed wrongly as non-A, non-B hepatitis. After advent of tests for hepatitis C and E are available NAFLD is more accurately defined. The term NAFLD is used to describe a wide spectrum of fatty liver changes ranging from fatty liver and steatosis on one side, to non-alcoholic steatohepatitis (NASH) and cirrhosis on the other[28]. Initially it was thought to be a mild disease with little clinical significance but at present NAFLD is recognised as a major cause of cryptogenic cirrhosis.

NOMENCLATURE AND CASE DEFINITION

NAFLD is deposition of fat in the liver of a non-alcoholic subject, a condition which may progress to end-stage liver disease. The spectrum

of progression of NAFLD is similar to alcoholic liver disease but is not caused by chronic alcohol consumption.

There is no standard definition of lean NAFLD and BMI cut-off points for overweight and obesity are not uniform across the world. Studies have shown that for a given BMI, Asians generally have a higher proportion of body fat than do Europeans[29]. Asian populations have also been shown to have an elevated risk of type 2 diabetes mellitus (DM), hyperlipidaemia and hypertension at a relatively low level of BMI. Therefore the recommended BMI cut-off points for Asians for defining overweight (22.9–25 kg/m2) and obesity (>25 kg/m2) are lesser than those of Western populations[29]. The term “lean NAFLD” is used to describe fatty liver in patients who are not overweight or obese, as per region-specific BMI. Therefore NAFLD with BMI <22.9 kg/m2 for Asian populations and <25 kg/m2 for non-Asian populations are considered non-obese NAFLD.

EPIDEMIOLOGY OF NAFLD

NAFLD has been reported worldwide but geographic variations in prevalence are evident. Although the worldwide prevalence has not yet been determined, NAFLD is highly prevalent in all continents but the highest rates being reported from South America (31%) and less common in Africa (14%), prevalence in Asia is reported to be 27%. In India prevalence has been reported to 30.7%[11]. NAFLD affects all racial and ethnic groups and has no age or sex predilection.

NAFLD is the cause of asymptomatic elevation of aminotransferases in 42–90% of cases once other causes of liver disease are excluded.

Globally the reported prevalence of non-obese NAFLD varies widely ranging from 3% to 30%. The prevalence data on non-obese NAFLD between the East and West are not directly comparable at least in part because of the different body mass index (BMI) cut-off values for Asians.

The prevalence of NAFLD in lean individuals varies widely among studies[30]. The variability is driven by a number of factors such as varying case definitions for NAFLD, varying methods used to diagnose NAFLD, varying study design, as certainment bias and true differences

from region to region. It is now apparent that there are not only differences from country to country but even from rural to urban areas, especially in the Asian subcontinent[31]. Unfortunately the published literature does not systematically evaluate the presence of specific Etiology that can drive NAFLD in lean individuals and future studies are needed to define the role of specific Etiology within these populations. Overall the global trends of NAFLD prevalence in lean individuals track the march of the obesity pandemic globally[32]. Even within the normal body mass index(BMI) range, there is an ongoing increase of obesity worldwide which is linked to expanded, dysfunctional and inflamed adipose tissue[33]. In cross-sectional studies, 7–20% of individuals with NAFLD have a lean habitus. Initially described in Asian populations and considered as a “third world phenotype”, this subset of NAFLD has since been described in other populations, including in Europe and the USA[31,34]. In Asia, the prevalence of NAFLD has been reported to vary from 12.6% of unselected patients to 27% of lean individuals[35-37]. A magnetic resonance (MR) spectroscopy-based study from Hong Kong reported a 19% prevalence of fatty liver in non-obese individuals compared to 61% in people with higher BMI[15]. Lean, non-alcoholic, non-diabetic, non-smoking Asian Indians in comparison to age, sex and BMI matched Caucasians, Hispanics, Blacks and Eastern Asians have been reported to have a 2-fold increased prevalence of hepatic steatosis, reflecting a poorer metabolic status in these individuals[38]. The NHANES study reported a prevalence of NAFLD of 7.9% in lean individuals in the USA[39,40], whereas an ultrasound-based study from Italy reported a 16% prevalence of lean NAFLD[5].

In a population-based study that included 565 adults from Hong Kong with repeat proton MR spectroscopy carried out at a mean interval of 47 months 71% of individuals were lean at baseline. A total of 7.9% had developed fatty liver at follow-up, which was associated with increasing BMI as well as waist circumference and triglycerides while remaining below the BMI boundaries for obesity[41]. Similar data have been reported from China[37,42]. In general, these data suggest a 3–5% annual incidence rate for NAFLD in lean individuals, which is mostly

associated with expansion of fat mass and increasing adiposity, underscoring the common linkage between adiposity and insulin resistance across various BMI strata among those with NAFLD. The prevalence of nonobese NAFLD described in the literature is summarized in Table1

Table 1. Prevalence of Nonobese NAFLD[43,44]

Study	Population	N	Detection	BMI cut-off value, kg/m	Nonobese NAFLD	MS among non-obese NAFLD
Fan et al, 2005	China, population-based	3175	US	<23	3.3	NA
Das et al, 2010	India, community-based	1911	US, LB	<23	6.9	26 %
Sinn et al, 2012	Korea, community-based (nonobese, nondiabetic)	5878	US	<23	27.4	23.64 %
Omagari et al, 2002	Japan, community-based (nonobese, nondiabetic)	3432	US	<25	12.5	NA
Kim et al, 2004	Korea, community-based (nonobese, nondiabetic)	768	US	<25	16.1	NAFLD was associated with components of MS in non-obese individuals
Chen et al, 2006	Taiwan, population-based	3245	US	<25	4.2	NA
Park et al, 2006	Korea, community-based	6648	US	<25	9.8	NA
Dassanayake et al, 2009	Sri Lanka, population-based	2985	US	<25	16.7	NA
Fu et al, 2009	Taiwan, community-based (adolescents)	220	US	<85th percentile	16.0	NA

Kwon et al, 2012	Korea, community-based	29994	US	<25	12.6	NAFLD was associated with higher risk of components of MS regardless of gender and obesity
Xu et al, 2013	China, community-based	6905	US	<25	7.3	Components of MS were separately associated with NAFLD
Lankarani et al, 2013	Iran, population-based	819	US	<25	9.2	NA
Wei et al, 2015	Hong Kong, community-based	911	MRS	<25	19.3	37.8
Younossi Z M et al,2012	NHANES III, USA	11613	USG	<25	17.29	NA
Bugianesi E et al, 2005	Selected cohort non-obese and non diabetic, Italy	12	Liver histology	NA	NA	Insulin resistance seen in all
Feldman A et al, 2016	Hospital based, Austria	187	USG	<25	29.41	Lean NAFLD showed significant impairment in glucose tolerance

ETIOLOGY OF NAFLD IN LEAN INDIVIDUALS

There are multiple causes of NAFLD in those who are not overweight or obese. The distribution of these causes varies with regional variances in the prevalence of these conditions and the type of clinical centre where such patients are seen. It is recognised that many individuals have none of these conditions especially in populations that are predominantly lean such as those in Asia. However, the existing literature finds that the pathobiology tracks that are seen in obese individuals in such cases and thus does not represent a unique

aetiology but rather a clinical sub-phenotype of “garden-variety” NAFLD associated with increasing adiposity, particularly in the visceral compartment. The majority of lean patients have underlying insulin resistance[43].

Table 2: **Causes of NAFLD in non-obese individuals[43].**

1. Genetic disorders:
(a) Abetalipoproteinemia
(b) Lipodystrophies
(c) Cholesterol ester storage disease
(d) Wolman disease
(e) Wilson’s disease
(f) PNPLA3 mutation*
2. Metabolic:
(a) Insulin resistance and increased visceral adiposity (most common cause)
3. Infectious-Inflammatory disorders:
(a) Celiac disease
(b) Small intestinal bacterial overgrowth

GENETICS

Some specific genetic disorders, particularly associated with adipose tissue or affecting specific metabolic pathways that result in fat accumulation in the liver despite physiological levels of lipid flux through the liver. These genetic disorders[45] include abetalipoproteinemia[46] hypobetalipoproteinaemia[47] familial combined hyperlipidaemia[48], Glycogen storage disease[49], Weber–Christian syndrome[50], and lipodystrophy[51].

PNPLA3 gene mutation, this is associated with the development of NASH rather than NAFL and its progression to cirrhosis and hepatocellular carcinoma. The prevalence of this mutation is variable; it is very common in the Hispanic communities and in certain Asian countries but not others[52].

DIET AND OTHER ENVIRONMENTAL INFLUENCES

In a Study among Chinese population, no substantial qualitative differences in diet were noted between those who were lean and had NAFLD versus obese individuals with NAFLD[53].

In general, even within the lean population, those with NAFLD tend to consume greater total calories[54].

MICROBIOME AND METABOLOMICS

There is now a substantial body of literature indicating a key role for the intestinal microbiome in the regulation of metabolic homeostasis. The composition of the microbiome is affected by age, gender, race, hormonal status and diet. Multifaceted changes occur in the microbiome with the onset of obesity[43].

A study of relatively small sample of individuals in Brazil revealed a trend towards qualitative differences compared to the obese NAFLD group, with a 3- fold lower abundance of Fecalibacterium and Ruminococcus species, and a relative deficiency in Lactobacillus[48].

VISCERAL OBESITY

BMI does not capture all aspects of adiposity and can be normal despite increased total body adipose tissue. Apparently normal Asian males with a BMI of 22kg/m2 had significantly higher total body and visceral adipose tissue[55]. The visceral adipose tissue size, including both intra-abdominal and epicardial fat compartments, are well known risk factors for cardiometabolic disease[56,57].

Visceral adipose tissue preferentially express 11β hydroxylase, a key enzyme in steroid synthesis which may explain a greater propensity for insulin resistance to develop in this compartment[30,44].

Adipocyte turnover studies have indicated that the overall size of the adipocyte mass has a higher set-point at turnover equilibrium in obese individuals than in lean individuals during childhood and adolescence, although the turnover in adulthood is similar in both lean and obese individuals. In adulthood, hypertrophy is the principal mechanism for expansion of the adipose tissue mass. The age-dependence of mechanisms by which adipose tissue mass expands may be relevant in various socio-economic contexts. For example, in economically

developing nations, access to excess calories often occurs in adulthood following long periods of childhood malnutrition, whereas dietary excess and diet-induced obesity often develop during childhood in the West. The precise mechanisms by which these differing mechanisms contribute to altered adipocyte biology, lipid trafficking, insulin sensitivity and propensity for adipose tissue inflammation in lean versus obese individuals remain to be defined[43].

Multiple studies in Asia and Europe revealed a relationship between low muscle mass and the increased risk of NAFLD[58,59]. Decreased muscle mass may impact development of NASH by impairing fat utilisation and reducing the body's ability to clear glucose.

METABOLIC

The metabolic characteristics of lean NAFLD subjects vary across ethnicities. A study revealed that lean, non-alcoholic, non-diabetic, non-smoking Asian Indians in comparison to age, sex and BMI matched Caucasians, Hispanics, Blacks and Eastern Asians–had a 2- to 3-fold increase in IR and 2-fold increase in hepatic steatosis[38]. Vos et al[36] reported that compared with obese NAFLD patients, lean NAFLD patients were younger, mostly male, and displayed lower fasting glucose, glycated haemoglobin and blood pressure values. Using data from NHANES III, Younossi et al[39] found that lean NAFLD was associated with younger age, female sex, and a decreased chance of having IR and hypercholesterolemia. A slight male preponderance has been found in the majority of studies on lean NAFLD, with the age ranging between 19 years and 56 years.

Lean individuals with NAFLD have a higher HOMA-IR and circulating triglyceride levels compared to lean individuals without NAFLD confirming the relationship between NAFLD and insulin resistance[17,39]. Compared to lean healthy controls, lean NAFLD patients have higher BMI, blood pressure, fasting blood sugar, and higher prevalence of dyslipidaemia and MS.

The mechanisms of insulin resistance in lean individuals are generally considered to be similar to those in obese individuals. A Chinese study

identified NAFLD without obesity to be a significant risk factor for diabetes mellitus and metabolic syndrome[21].

Insulin Resistance

IR is an important trigger for initiation of NAFLD. NAFLD has been shown to be associated with IR independently of BMI[60] and studies have reported that IR is present in a significant proportion of lean NAFLD patients even without other metabolic risk factors[19,61]. A study revealed that lean, non-alcoholic Asian Indians had 2- to 3-fold increase in IR in comparison to matched Caucasians, Hispanics, Blacks and Eastern Asians[38]. However, IR is not universally present in all lean NAFLD patients. Several studies have revealed that lean NAFLD patients have little or no IR.

A study has reported that patients with NASH have severe adipose tissue IR independent of the degree of obesity[62]. In a recent study, Feldman et al[63] have found that lean subjects with NAFLD are insulin resistant and have evidence of dysfunctional adipose tissues.

Dyslipidaemia

Several studies have revealed a frequent occurrence of dyslipidaemia in lean NAFLD patients[17,18,39,64]. The liver plays an important role in lipid metabolism and may be involved in the development of dyslipidaemia in NAFLD[64]. Impaired hepatic lipid handling may occur in patients with NAFLD, causing faulty lipid homeostasis and initiation of dyslipidaemia. Individuals with dyslipidaemia without obesity are termed as normal weight dyslipidaemia. The estimates of prevalence of normal weight dyslipidaemia in the general population range from 10% to 37%[65].

Several new studies suggest an important role of intrahepatic fat in the development of dyslipidaemia and IR in humans[66,67].

A study by Kim et al[68] demonstrated that triglyceride levels were significantly associated with both the development and regression of NAFLD among non-obese Koreans. Oxidized low-density lipoprotein (LDL) is a powerful immunogenic molecule, which causes oxidative stress and produces antibodies (i.e., oxLDL-ab). A study has revealed that oxLDL-ab/HDL ratio is associated with severity of hepatocellular

ballooning and liver fibrosis in lean NAFLD patients. This ratio could play an important role in distinguishing mild from severe states of NAFLD[69].

Table 3. Demographic and metabolic profiles of lean NAFLD patients in different studies

Study, Country	*N*	Age* (years)	Male: Female	BMI* (kg/m^2)	WC* (cm)	DM (%)	HOMA-IR*	HTN (%)	AST/ALT* (IU/L)	Serum Chol/TG/HDL* (mg/dL)
Younossi et al[39] USA	431	42	187:244	22.1	NA	6.7	2.7	17.8	21/17	NA
Honda et al[20] Japan	134	56	57:77	22.8	NA	32	3.4	NA	47/70	213/144/57
Feng et al[21] China	134	48	72:62	22.7	82	15	2.1	34	21/21	5.2/1.7/1.4#
Alam et at[18] Bangladesh	119	41	62:57	23.0	87	26	1.9	21	43/52	202/243/36
Kumar et al[17] India	27	38	19:08	21.7	80	3.7	1.7	15	38/45	203/190/40
Leung et al[16]Hong Kong	29	56	13:16	22.1	79	52	NA	41	25/45	3.7/1.4/1.5#
Kim et al.,[19] Korea	74	51	48:26	23.4	83	10	2.6	43	23/31	208/194/44

Study, Country	*N*	Age* (years)	Male: Female	BMI* (kg/m^2)	WC* (cm)	DM (%)	HOMA-IR*	HTN (%)	AST/ALT* (IU/L)	Serum Chol/TG/HDL* (mg/dL)
Bhat et al[70] India	30	39	NA	21.7	84	NA	3.5	NA	NA/69	177/185/38
Akyuz et al[71] Turkey	37	41	26:11	23.6	NA	27	2.8	NA	49/82	211/167/47
Margariti et al.[72] Greece	19	19	11:08	<25	94	5	NA	16	45/92	223/145/51

*Data expressed in mean or median. NA: Data not available. #Data in mmol/L.

PATHOGENESIS OF NAFLD IN LEAN INDIVIDUALS

The broad pathogenic basis for NAFLD and its more aggressive phenotype NASH is now established[73]. NAFLD typically develops in a systemic milieu characterised by diet-induced adiposity, increased gut permeability, altered microbiome, insulin resistance, systemic inflammation and an acute phase reaction where the liver is exposed to excess metabolic substrates (lipids and carbohydrates), pro-inflammatory bacterial products and cytokines (Fig.1). These factors cause hepatocellular stress pathway activation resulting in cell death and activation of inflammatory signalling. Sustained inflammation drives fibrogenic remodelling towards cirrhosis. Simultaneously, regenerative signals are activated. Disease progression reflects a balance between factors driving the disease towards cirrhosis or restoration of normal function and structure.

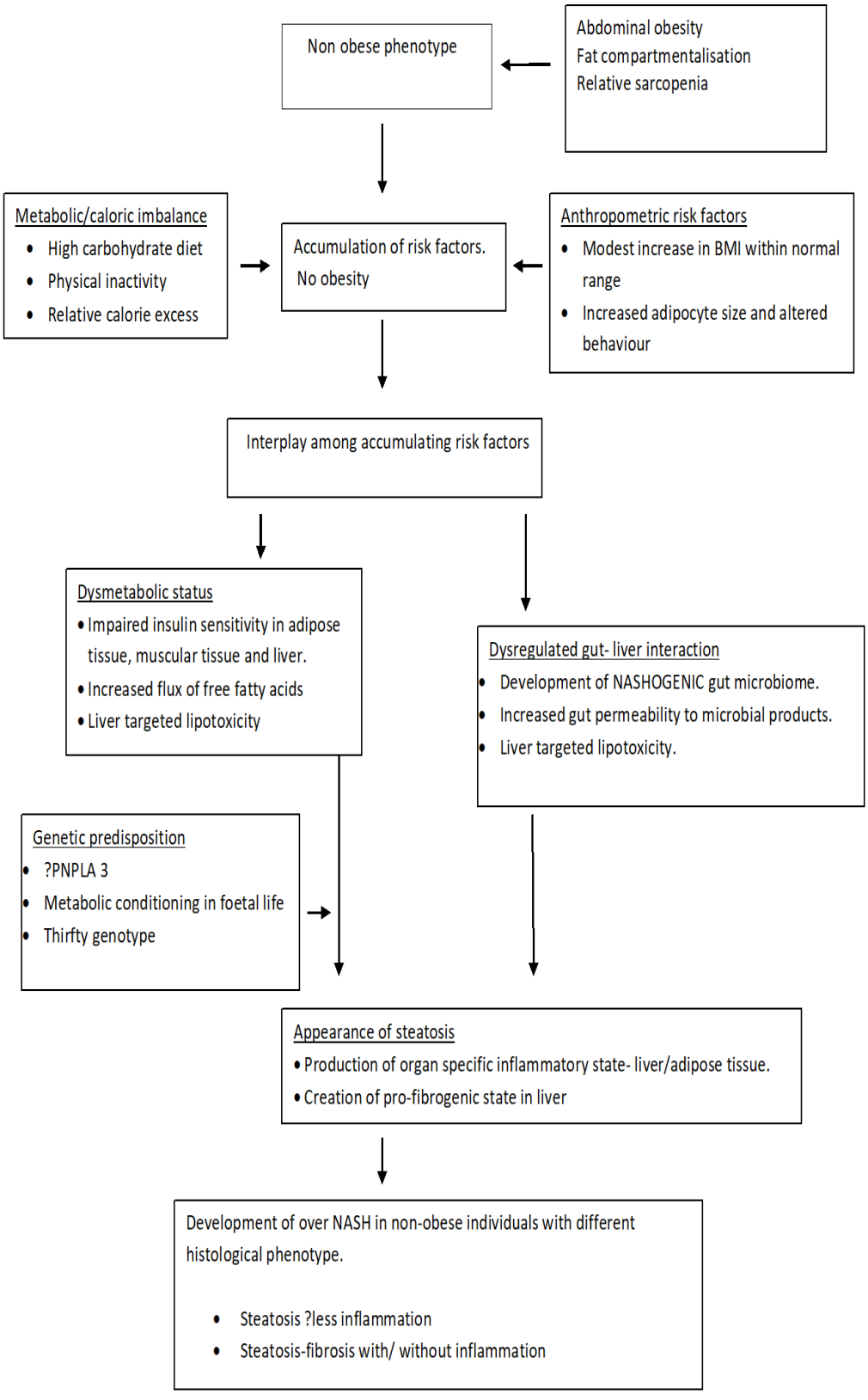
Non obese phenotype
Abdominal obesity
Fat compartmentalisation
Relative sarcopenia
Metabolic/caloric imbalance
High carbohydrate diet
Physical inactivity
Relative calorie excess
Accumulation of risk factors.
No obesity
Anthropometric risk factors
Modest increase in BMI within normal range
Increased adipocyte size and altered behaviour
Interplay among accumulating risk factors
Dysmetabolic status
Impaired insulin sensitivity in adipose tissue, muscular tissue and liver.
Increased flux of free fatty acids
Liver targeted lipotoxicity
Dysregulated gut- liver interaction
Development of NASHOGENIC gut microbiome.
Increased gut permeability to microbial products.
Liver targeted lipotoxicity.
Genetic predisposition
?PNPLA 3
Metabolic conditioning in foetal life
Thirfty genotype
Appearance of steatosis
Production of organ specific inflammatory state- liver/adipose tissue.
Creation of pro-fibrogenic state in liver
Development of over NASH in non-obese individuals with different histological phenotype.
Steatosis ?less inflammation
Steatosis-fibrosis with/ without inflammation

Fig 1. Pathogenesis of NAFLD in non-obese individual.[43]

The underlying pathophysiologic basis of NAFLD in lean subjects remains uncertain. It appears that there is no single pathway to this multifactorial phenotype. Genetic predisposition acting together with environmental influences, such as dietary composition and gut microbiome may have an important role. Polymorphisms in genes affecting lipid metabolism, oxidative stress, IR and immune regulation have been identified as predisposing factors for the development of NAFLD. The peripheral IR might contribute to steatosis by increasing lipolysis and delivery of free fatty acids to the liver. It is likely that multiple hits, acting together on genetically predisposed lean subjects induce NAFLD.

Development of steatosis and steatohepatitis

The precise mechanism of development of steatosis and steatohepatitis depends on the specific aetiology underlying the development of the condition in a lean individual. Hepatic steatosis results when triglyceride synthesis exceeds its utilisation and export. Lean individuals with increasing adiposity and insulin resistance are likely to recapitulate this pathophysiology.

Lower lyso-PC concentrations were found in lean NAFLD. Low levels of lyso-PCs have been linked to obesity[74], and hypertriglyceridemia[75],

The hallmark of NASH is the development of hepatocellular ballooning, which is associated with disruption of cytoskeletal architecture and accumulation of ubiquitinated compounds that cannot be eliminated because of proteasomal dysfunction.[76] However ubiquitin staining is present even in cells that are not ballooned, suggesting that the histological manifestation of ballooning is a late feature that follows progressive intracellular architectural and proteasomal dysfunction. There are currently no data to indicate that unique mechanisms come into play in the development of hepatocellular ballooning in lean individuals with steatohepatitis.

Fibrosis and fibrogenic remodelling of the liver are also downstream events.

Currently it is believed that progressive NASH in lean individuals involves activation of pathways similar to those in obese individuals

and that disease progression is linked to quantitative differences involving genetic, dietary, molecular and cellular changes in various organs in a given individual[43].

Natural history and progression to cirrhosis

A multiethnic NAFLD cohort from the USA revealed that liver disease progression was less rapid in non-obese individuals[56]. Although the proportion of those with advanced fibrosis was similar, liver failure, hepatocellular carcinoma and overall mortality were lower in those with non-obese versus obese NAFLD.

A recent study by Hagström et al[77] reported that lean patients are at higher risk of developing severe liver disease(HR 2.69; p = 0.007)compared to patients with NAFLD and a higher BMI (HR1.11; p= 0.74), independent of available confounders.

In 2014, a study found that the cumulative survival was significantly shorter in lean patients with NAFLD compared to non-lean patients with NAFLD over a follow-up period of 133 months[78]. They also reported a lower fibrosis stage in the lean population.

In general, patients with lean NAFLD tend to have less severe disease compared to obese patients (Table 4). Kumar et al[17] reported that the mean NAFLD activity score in lean NAFLD patients was significantly lower than that in obese NAFLD patients (3.3 ± 1.5 vs. 4.1 ± 1.4, $p < 0.001$). However, 28% of the lean NAFLD patients met the criteria for NASH which was statistically similar to the prevalence of NASH in the obese NAFLD (38%) patients. The proportion of patients with hepatic fibrosis was significantly lower in the lean NAFLD patients compared to the obese NAFLD patients (50% vs. 84%, $p < 0.01$).

In a recent large series from Hong Kong[16] histological severity and clinical outcome of 72 non-obese (BMI <25 kg/m^2) NAFLD patients were compared with 235 obese NAFLD patients. Compared with obese patients, non-obese patients had lower NAFLD activity score (3.3 ± 1.3 vs. 3.8 ± 1.2; $p = 0.019$) and lower fibrosis stage (1.3 ± 1.5 vs. 1.7 ± 1.4; $p = 0.004$). Only elevated serum triglyceride level was independently associated with higher NAFLD activity score (odds ratio: 1.6). Other studies have also reported a lower histological severity in

lean NAFLD patients compared to obese NAFLD patients[20,36,71]. A study from Bangladesh found no significant difference between histology of lean and obese NAFLD cases[18].

In study by Leung et al[16], compared to obese patients nonobese patients had lower NAFLD activity score (3.3 ± 1.3 vs. 3.8 ± 1.2; P = 0.019), mainly contributed by steatosis (1.7 ± 0.8 vs. 2.0 ± 0.8; P = 0.014) and presence of hepatocyte ballooning (60.9% vs. 73.4%; P = 0.045). Similarly, nonobese patients had lower fibrosis stage (1.3 ± 1.5 vs. 1.7 ± 1.4; P = 0.004), serum cytokeratin-18 fragments (283 vs. 404 U/L; P < 0.001) and liver stiffness measurement by transient elastography (6.3 vs. 8.6 kilopascals; P < 0.001). By multivariate analysis in nonobese patients, only elevated serum triglyceride level was independently associated with higher NAFLD activity score[16].

In study by Margariti et al[72] Liver stiffness values by transient elastography were significantly lower in patients with normal than in those with increased BMI (5.0 ± 1.6 vs. 9.5 ± 8.7 kPa; P=0.003). In the 56 patients with liver biopsy, the prevalence of nonalcoholic steatohepatitis (50% vs. 68.8%; P=0.423) and the severity of inflammation and fibrosis did not significantly differ between cases with normal and those with increased BMI.

Table 4 Histological severity of lean NAFLD compared to obese NAFLD

Study	Lean / Obese	Fibrosis		Advanced Fibrosis > F2	
		Lean	Obese	Lean	Obese
Leung *et al*[16].	72/235	1.3 ± 1.5	1.7 ± 1.4* (significant)	26.1%	27.7%
Alam *et al*[18].	56/164	1.2 ± .8	1.1 ± 0.8	19.6%	18.9%
Kumar *et al*[17].	18/73	01 (0–04)	02 (0–04)* (significant)	5.6%	27%
Akyuz *et al*[71].	37/446	0 (0–1)	1 (0–2)* Significant	0	0

*Significantly different between lean and obese.

CLINICAL IMPLICATIONS OF NON-OBESE NAFLD

Very little information is available about natural history, prognosis and therapeutic strategies in lean subjects with NAFLD.

A large pooled analysis found a U-shaped association between BMI and the risk of death in East Asians. Overall the risk of death among Asians as compared with Europeans seems to be more strongly affected by a low BMI than by a high BMI[79]. Dela Cruz et al[78] followed-up 1,090 NAFLD patients, 125 (11.5%) of who were lean for 133 months and found that the cumulative survival was significantly shorter in patients with lean NAFLD compared to those with non-lean NAFLD.

A recent study from Hong Kong has revealed that non-obese NAFLD (*n* = 72) patients tend to have less severe disease and may have a better prognosis than obese patients (*n* = 235)[16].

DIAGNOSIS

Symptoms as with many other types of chronic liver disease, most patients with NAFLD (48–100%) are asymptomatic. The liver disease is often discovered incidentally during routine laboratory examination when a hepatic panel reveals an elevated ALT level. NAFLD is the most common cause for unexplained persistent elevation of ALT levels once hepatitis C and other chronic liver diseases have been excluded. When symptoms occur they are usually nonspecific. Vague right upper quadrant abdominal pain, fatigue, and malaise are the most common of these nondescript symptoms. Rarely, pruritus, anorexia, and nausea may develop. Jaundice, abdominal distension (ascites), gastrointestinal bleeding, and confusion (encephalopathy) are all indicative of advanced liver disease (decompensated cirrhosis), occurring late in the course[80].

Table 5: Step wise approach to diagnosis of NAFLD

	FINDINGS	FOLLOW UP ACTION
1	Identification of NAFLD and/or NASH	Rule out alcoholism
2	Raised ALT in high risk groups	History from patient relatives
3	Fatty liver on USG or imaging	Random blood alcohol level
4	Exclude other causes like viral, autoimmune, metabolic, etc.	MCV for B12 and/or folic acid deficiency.
5	Liver biopsy (required for diagnostic documentation	AST/ALT ratio, mitochondrial AST/total AST ratio

Biochemical parameters.

Lab parameter

4-5 fold increase in ALT and AST levels, ALT/AST ratio alterations (ALT/AST ratio usually< 1 in cirrhosis, < 2 in alcoholic liver disease).

2-3 fold increase in alkaline phosphatase.

GGT is usually normal, upto 2-3 fold rise in some cases.

Bilirubin increases in late stages of NAFLD, albumin decreases in late stages of NAFLD.

Prothrombin time increases in late stages of NAFLD

S.ferritin raised in upto 50% cases, S. iron is raised and transferrin saturation decreases.

Lipids raised in underlying hyperlipidaemia.

Viral markers to exclude viral hepatitis

DIAGNOSIS OF NAFLD BY IMAGING:

Non-invasive radiological imaging studies such as USG, CT scan of abdomen, and MRI may help in diagnosis of fatty infiltration of liver; but they do not distinguish between fatty liver, steatohepatitis and steatohepatitis with fibrosis – for which liver biopsy is required.

A.USG FINDINGS IN NAFLD:

Increased echogenicity or (hyperechogenic) liver.

Increased liver contrast compared to kidney.

Vascular blurring – mainly of hepatic veins.

Attenuation of echogenic level in deep-seated areas.

USG examination is to be performed first as it is the least expensive and carries no risk of radiation. Its sensitivity is more, but it lacks specificity.

Ultrasound gradings of fatty liver [81]:

Grade I: echogenicity is just increased.

Grade II: when the echogenic liver obscures the echogenic walls of portal vein branches.

Grade III: echogenic liver obscures the diaphragmatic outline.

B. FIBROSCAN

Non-invasive valuable procedure in the diagnosis of liver stiffness/fibrosis. Application of Fibroscan can examine liver stiffness. Diagnosis of liver stiffness and fibrosis by this method has been reported previously. Fibroscan was first described in France and then in other parts of the world[82].

In recent years, substantial attention has been focused on one dimensional transient elastography (TE). TE is a non-invasive ultrasound-based method that uses shear wave velocity to assess tissue (*e.g.*, liver) stiffness. Shear (secondary or S-) waves were initially discovered in seismology as slow waves that follow the primary compressional wave, hence their name. They are the manifestation of elastic waves that travel through the body of an object, as opposed to the surface waves, which, as the name implies, travel on the surface. In contrast to sound waves, which are longitudinal, shear waves are transverse, thus the motion of the affected tissue is perpendicular to the direction of wave propagation. As a result, shear waves move slowly (< 50 m/s) and are rapidly attenuated by liver parenchyma. This effect depends on the elastic properties of the tissue, with the speed of shear waves inversely proportional to the tissue elasticity. The method was designed at the Langevin institute in 1995 and was initially implemented for quality control in the food industry; however, since 2001, it has been applied in medical practice under the name FibroScan®[83].

Among the non-invasive tests, transient elastography (FibroScan®, TE) with controlled attenuation parameter (CAP) has demonstrated good accuracy in quantifying the levels of liver steatosis and fibrosis in patients with NAFLD, the factors associated with the diagnosis and NAFLD progression. The method is fast, reliable and reproducible, with good intra- and interobserver levels of agreement, thus allowing for population-wide screening and disease follow-up. The initial inability of the procedure to accurately determine fibrosis and steatosis in obese patients has been addressed with the development of the obese-specific XL probe. TE with CAP is a viable alternative to ultrasonography, both as an initial assessment and during follow-up of patients with NAFLD. Its ability to exclude patients with advanced fibrosis may be used to identify low-risk NAFLD patients in whom liver biopsy is not needed, therefore reducing the risk of complications and the financial costs.

TE assessment of liver fibrosis has predominantly been implemented in patients with chronic viral hepatitis, as well as patients with other chronic liver diseases of different etiologies. Recent studies have examined the usefulness of LSM compared with liver biopsy to identify fibrosis in NAFLD patients. Table 5 shows details of eight studies that have examined the usefulness of LSMs in the identification of different stages of liver fibrosis in NAFLD patients compared with liver biopsy. In these studies, for F ≥ 2, the LSM cut-off values range from 6.2 to 11 kPa, with 62%-90% sensitivity and 74%-100% specificity. For F ≥ 3, the LSM cut-off values range from 8 to 12 kPa, with 84%-100% sensitivity and 83%-97% specificity. For F4, the LSM cut-off values range from 9.5 to 20 kPa, with 90%-100% sensitivity and 75.9%-98.4% specificity.

Table 6 Usefulness of liver stiffness measurement in detection of fibrosis in nonalcoholic fatty liver disease patients[84]

Study	>/=F2		>/=F3		>/=F4	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Imajo et al (2016)	61.7	100	85.7	83.8	100	75.9
Pathik et al (2015)	NA	NA	90	80	90	80
Yoneda et al (2007)	81.8	91.2	87.5	84.3	100	98.4
Cassinotto et al (2015)	>/=90	NA	>/=90	NA	>/=90	NA
Wong et al (2010)	88	74	84	83	92	97
Lupsor et al (2010)	67	84	100	97	NA	NA
Yoneda et al (2008)	88	74	85	81	100	97
Kumar et al (2013)	78	79	85	88	90	88

MATERIALS AND METHODS

SOURCE OF DATA

Patients attending the Out Patient Department (OPD) and also admitted in gastroenterology ward of Dayanand Medical College and Hospital, Ludhiana

METHOD OF COLLECTION OF DATA

Non-obese OPD and IPD patients more than 18 years of age screened using USG for NAFLD were enrolled in this study.

INCLUSION CRITERIA FOR PATIENTS

- Patients with fatty liver diagnosed on basis of USG
- Patients more than 18 years of age with BMI <22.9 KG/M^2 as per Asian cut off for defining obesity.

EXCLUSION CRITERIA FOR PATIENTS

- Age</=18 years
- Body Mass Index (BMI)≥22.9 kg/m2
- Hepatitis B, Hepatitis C or HIV positive
- Consuming more than 20 grams per day of alcohol
- Taking medication containing corticosteroids, oestrogen, tamoxifen, amiodarone, antiretroviral medication, cannabis abuse.
- History of IV drug abuse.
- Extra hepatic cholestasis (based on ultrasound or total bilirubin ≥ 2).
- Evidence of liver SOL on ultrasonography.
- Ascites on ultrasonography.
- Pregnancy
- Congestive cardiac failure
- Chronic renal failure
- Stroke
- Ischemic heart disease

METHOD

All the patients falling in the sampling frame will be invited to participate in the study. Only those providing informed consent will be included in the assessment.

Non obese NAFLD patients were defined as those having BMI<22.9 kg/m^2 as per Asian cut offs for defining obesity and metabolic syndrome.

Demographic details (age, sex) will be obtained. Personal history related with exposure to risk factors (alcohol, smoking, etc.) were noted, medication history was enquired. Anthropometric measurements were performed and body mass index was calculated. A systemic examination (CVS, Respiratory, Per-abdomen and CNS) was performed.

Blood pressure measurements were done. Hypertension was defined according to NCEP-ATPIII criteria with hypertension defined as BP ≥130/85mmHg and also patients who were actively taking antihypertensive medications. A 2 ml blood sample of the patients was collected under aseptic conditions. The following haematological and biochemical assessments were performed:

1. Hemoglobin
2. Hematocrit
3. Fasting glucose
4. Fasting insulin
5. S. Lipid Profile (Total Cholesterol, Triglyceride, HDL-c, LDL-c)
6. S. Bilirubin (Total)
7. S. Bilirubin (Direct)
8. S. Alkaline Phosphatase
9. S. AST
10. S. ALT
11. S. Total Protein
12. S. Albumin
13. S. Urea
14. S. Creatinine
15. S. Sodium

16. S. Potassium

17. Thyroid stimulating hormone (TSH)

All blood investigations needed for this study were performed in biochemistry, pathology and microbiology labs in DMCH. All the patients underwent electrocardiographic assessment; Viral Markers (HBV, HBsAg, HIV) were assessed by ELISA. Chest X-ray PA view was performed. Fatty liver was defined on the basis of USG abdomen (hyperechoic liver where the echo-texture of the liver was brighter than the kidney, and had blurred vascular margins and deep attenuation of ultrasound signal) and was done by a single observer in Deptt. of Radiology, DMCH. On Ultrasound fatty liver was graded as: Grade I: echogenicity is just increased Grade II: when the echogenic liver obscures the echogenic walls of portal vein branches Grade III: echogenic liver obscures the diaphragmatic outline FibroScan was done in Deptt. Of Gastroenterology, DMCH (endoscopy complex) by a single observer on Echosens machine who measured liver fibrosis and liver steatosis. Grading of fibrosis was done: F0-F1 – 0-6 kpa F2 - 6.1 - 8kpa F3 – 8.1-10kpa F4 - ≥10kpa.

SAMPLE SIZE

All non obese NAFLD patients attending the OPD and admitted in gastroenterology department of DMCH within 1 year (March, 18 to march, 19) were enrolled in this study

OUTCOME

PRIMARY OUTCOME:

To determine frequency of fibrosis by Fibroscan in non-obese individuals of NAFLD.

SECONDARY OUTCOME:

Correlation of fibrosis in non-obese individuals of NAFLD with age, diabetes and hypertriglyceridemia.

STATISTICAL ANALYSIS

The data so collected was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical data was represented as frequencies and percentages. Continuous data was represented as Mean±SD. Chi-square test was used to compare the

proportions. Analysis of variance and Independent samples ‘t‘ test were used to compare the continuous data. The confidence level of the study was kept at 95% hence a ‘p‘ value less than 0.05 indicated a statistically significant association.

OBSERVATIONS AND RESULTS

The study was carried out to determine frequency of fibrosis by fibroscan in non-obese individuals of NAFLD and to study correlation of fibrosis in non-obese individuals of NAFLD with age, diabetes and hypertriglyceridemia. For this all non obese NAFLD patients attending the OPD and admitted in gastroenterology department of DMCH within 1 year (March, 18 to march, 19) were enrolled in this study, (total number patients were 121).

Table 7: Demographic profile of patients

SN	Characteristics	No of patients	Percentage
1	Age (years)		
	<40	28	23.14
	41-50	62	51.24
	>50	31	25.62
2.	GENDER		
	MALE	74	61.2
	FEMALE	47	38.8
3.	HYPERTENSIVE		
	YES	44	36.4
	NO	77	63.6
4.	DIABETIC		
	YES	48	39.7
	NO	73	60.3
5	HYPERTRIGLYCERIDEMIA		
	YES	64	52.9
	NO	57	47.1
6.	DYSLIPIDEMIA		
	YES	68	56.2
	NO	53	43.8

Age of patients ranged from 30 to 63 years.

Maximum number of patients were aged between 41-50 years (51.2%). Maximum numbers of patients were males 61.2% and females being 38.8%. 36.4% patients were hypertensive and 39.7% were diabetic. 52.9 % patients had hypertriglyceridemia and 56.2 % patient had dyslipidemia.

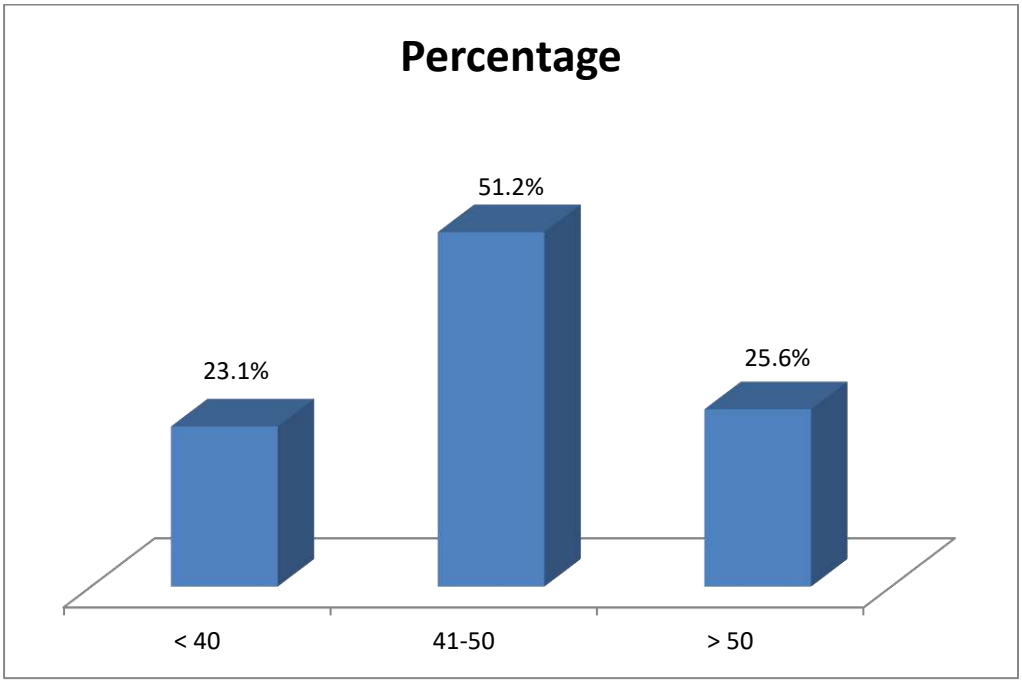

Fig 2: Distribution of patients as per age (in years).

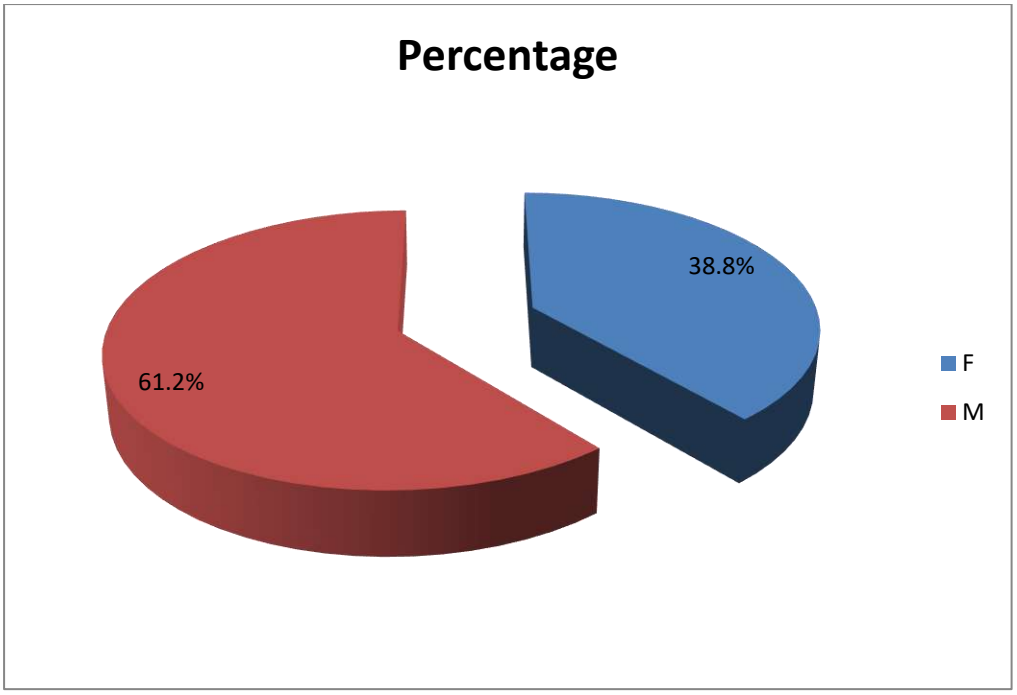

Figure 3: Distribution of patients according to gender.

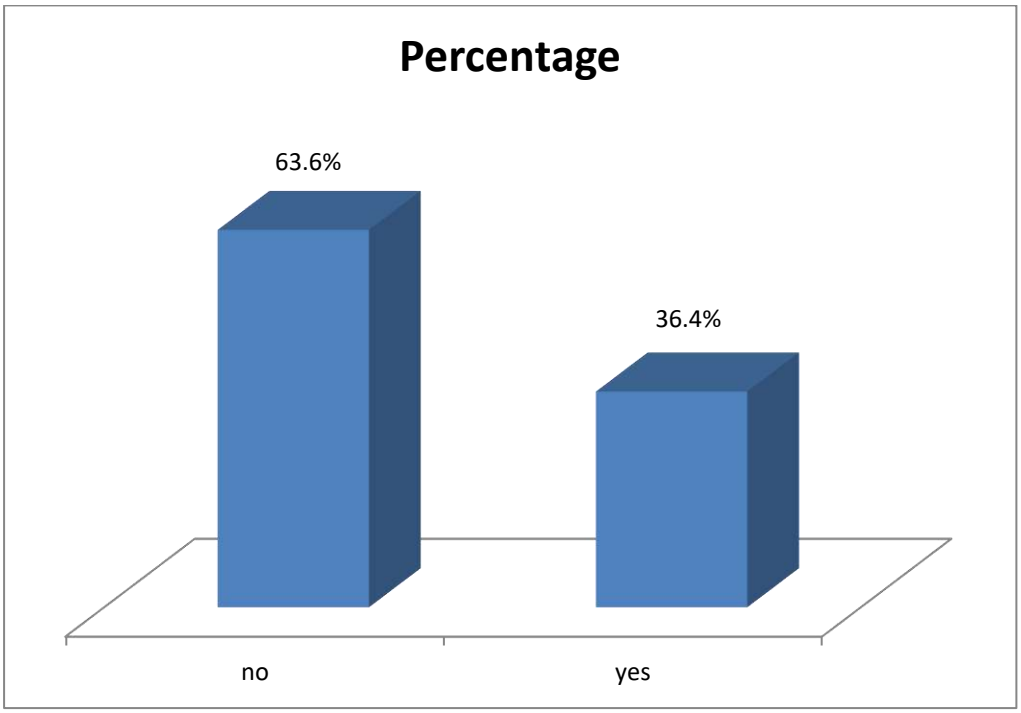

Figure 4: Distribution of patients according to hypertension.

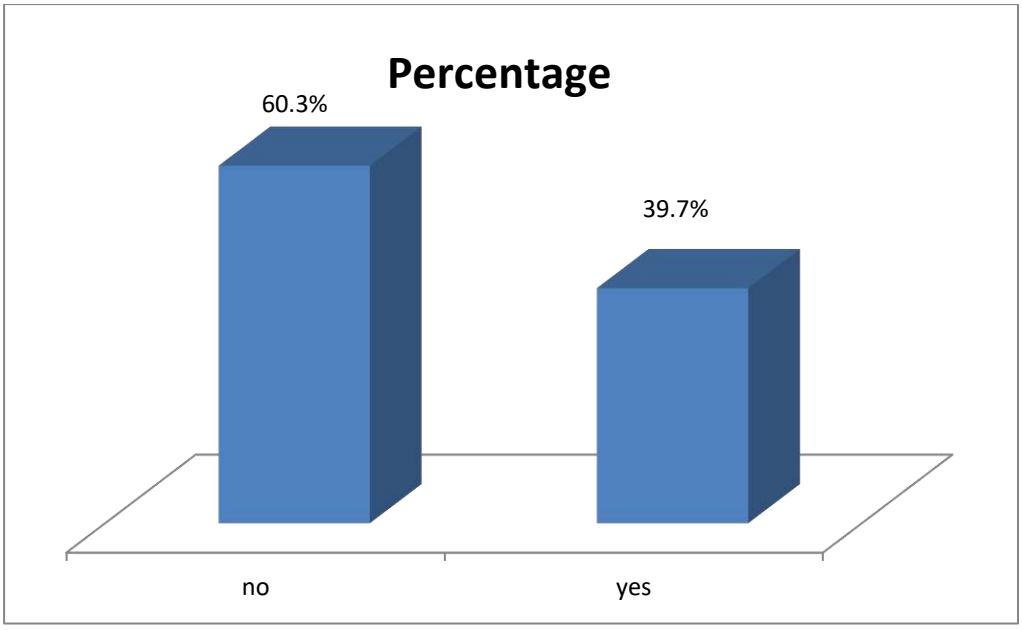

Figure 5: Distribution of patients according to diabetic status.

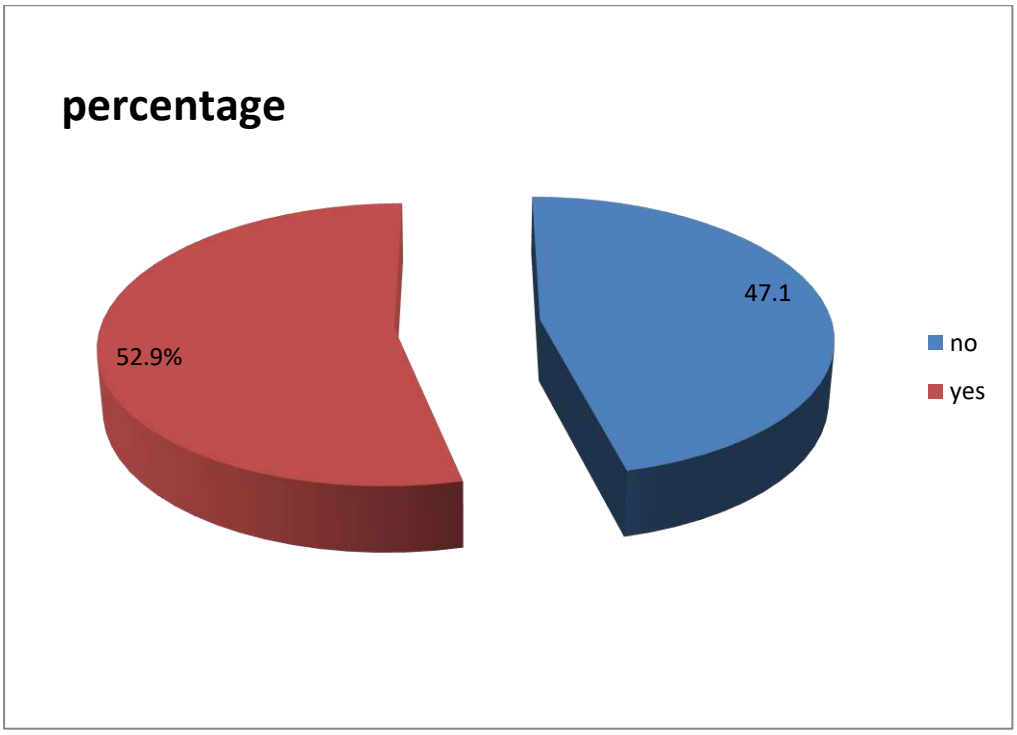

Figure 6: Distribution of patients according to hypertriglyceridemia.

Association between USG grading and fibrosis

All patients with significant fibrosis had USG grade III fatty liver.

83.30 % patients with moderate fibrosis (F2) had USG grade III fatty liver and 16.7 % had USG grade II fatty liver.

Fatty liver grade II and III on USG were seen in 64.70% and 35.3% patients respectively of mild fibrosis group.

None of the patients in fibrosis group had grade I fatty liver on USG.

Table 8: Distribution of cases according to USG Grade (n=121)

USG (FATTY LIVER GRADE)	No. of cases	Percentage
I	60	49.6%
II	44	36.4%
III	17	14.0%
Total	121	100.0%

Maximum number of cases were in grade 1 (49.6%).

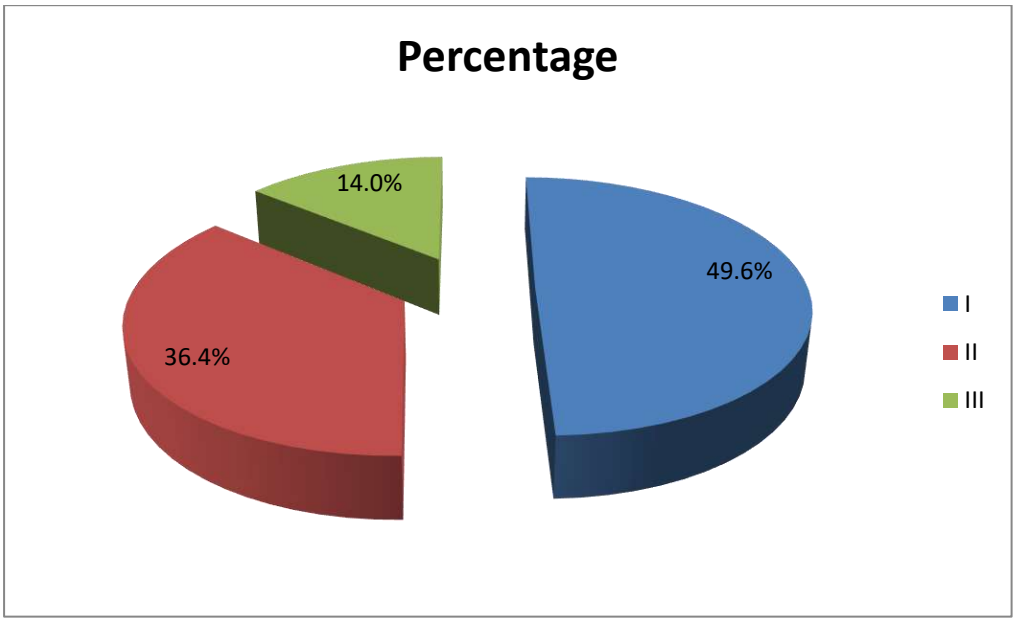

Figure 7: Distribution of cases according to USG Grade.

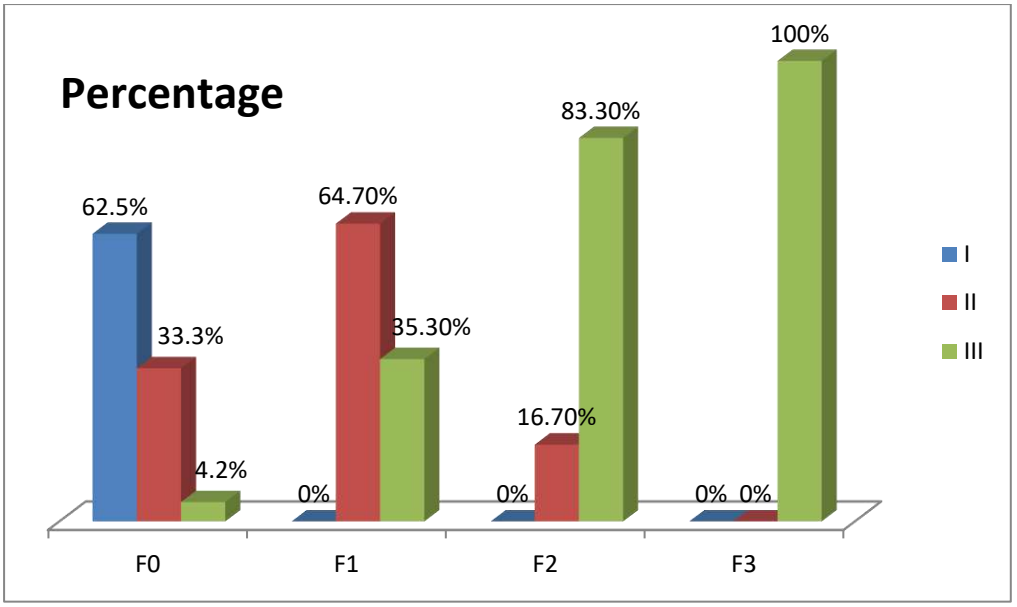

Fig 8 Association between USG grading and fibrosis grading

Frequency of fibrosis

Frequency of liver fibrosis (grade F1 and above) was 20.7 % in this study i.e. 25 out of 121 of non –obese NAFLD individuals had liver fibrosis.

Mean kPa value was 5.2 +/-0.79 in all non-obese NAFLD patients in the study

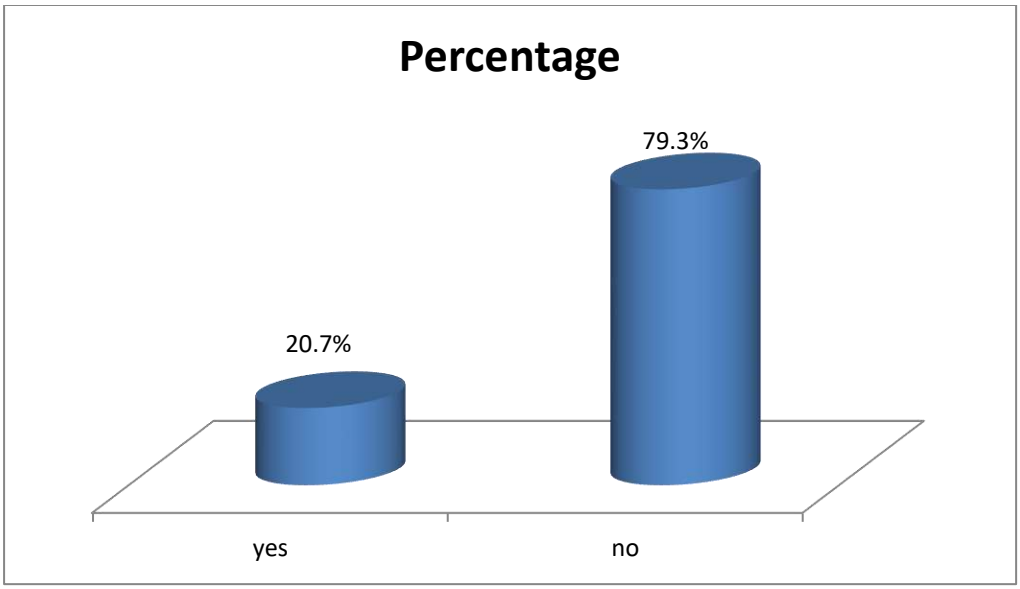

Fig 9: Distribution of cases according to presence or absence of fibrosis

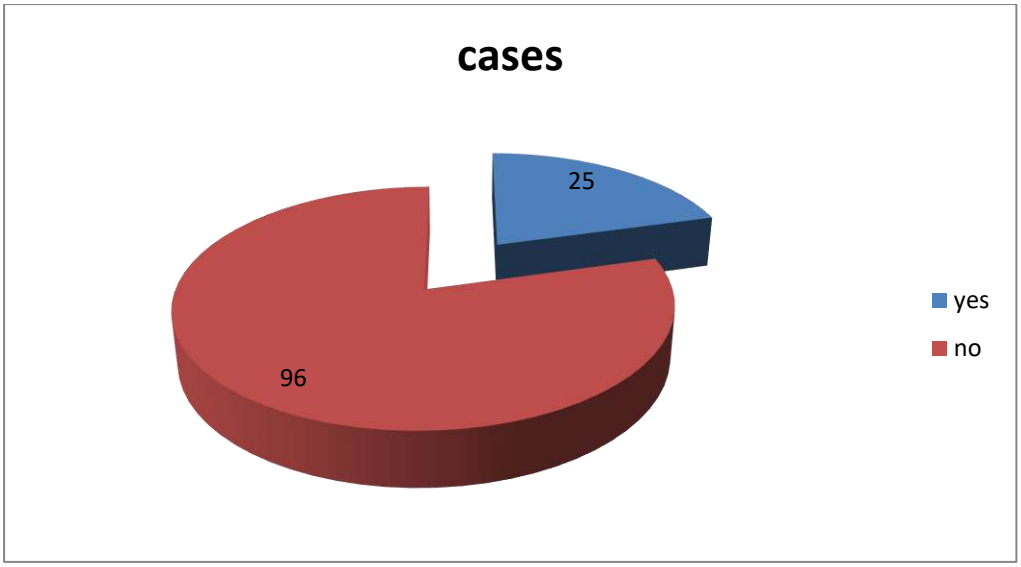

Fig 10: Distribution of cases according to presence or absence of fibrosis (cases)

Fibrosis grade

14% (17 out of 121) of patients had mild (F1) fibrosis.

5% (6 out of121) patients had moderate (F2) fibrosis.

1.7% (2 out of 121) patients had significant (F3) fibrosis.

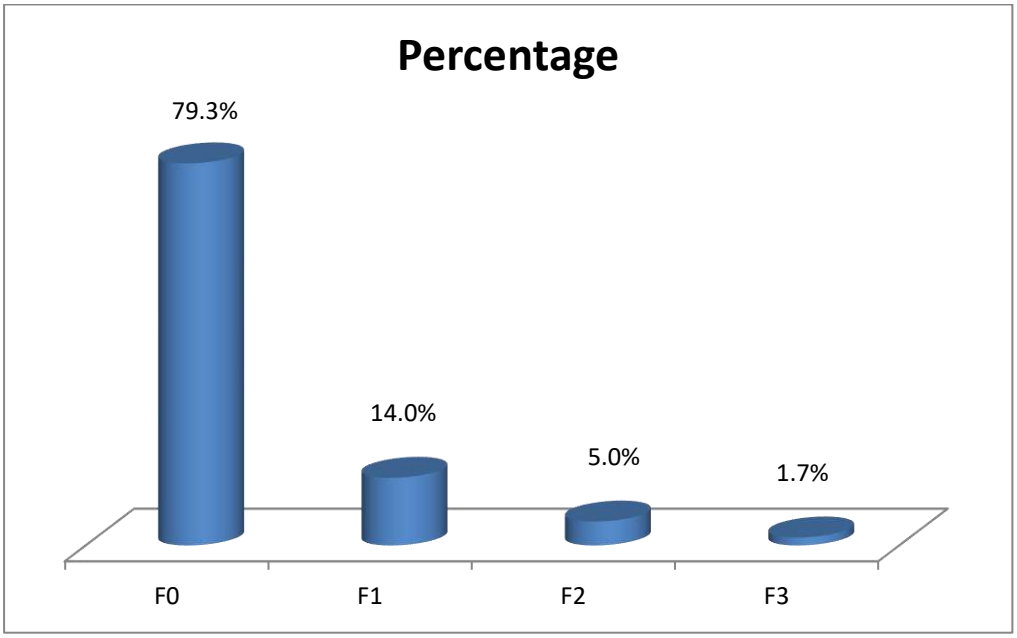

Fig 11: Distribution of cases according to fibrosis grade.

In patients with fibrosis (fibrosis grade F1 to F3, total patient 25) 11 (44%) were females and 14 (56%) were male.

In patients with mild fibrosis (F1) 35.3% were female and 64.7% were male. In moderate fibrosis group (F2) 66.7 % were female and 33.3% were male, whereas in significant fibrosis (F3) gender distribution was 50%.

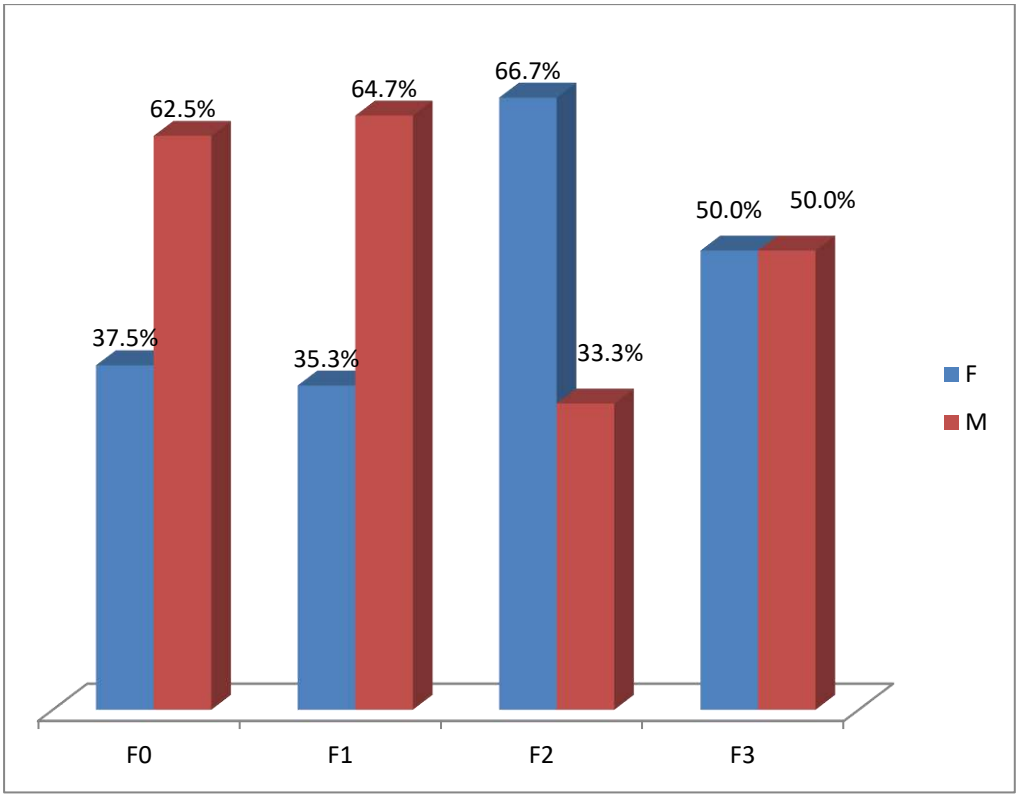

Fig 12: Distribution of cases according to fibrosis grade and gender.

Mean age in non-obese NAFLD patients with no fibrosis was 45.5 +/- 6.7 years.

In patients with fibrosis there was an increasing age trend with increase in severity of fibrosis (statistically significant, p value<0.05). Mean age being 44.6 +/- 5.4 years in F1 grade, 51.6 +/- 4.6 years in F2 and 61.5 +/- 1.2 years in F3 grade.

Table 9: Age distribution in different fibrosis groups of non-obese NAFLD.

	F0		F1		F2		F3		F value	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (in years)	45.56	6.76	44.65	5.41	51.67	4.63	61.50	2.12	5.7	<0.05

Table 10: Age distribution in different fibrosis groups of non-obese NAFLD.

Fibrosis grade	Mean age (Years)	Standard deviation
F0	45.5	6.7
F1	44.6	5.4
F2	51.6	4.6
F3	61.5	1.2

Association of fibrosis with diabetic status.

In patients with no fibrosis, 29.2 % patients had diabetes.

In patients with fibrosis 20 out of 25 (80%) patients had diabetes with increasing association with severity of fibrosis. 76.5 % patients with F1 grade, 83.3 % patients with F2 grade and all patients with F3 grade had diabetes.

There was a direct and significant association between diabetic status, fasting blood glucose levels and presence and grade of fibrosis (p value <0.05).

Table 11: Diabetic status among different fibrosis grades.

Diabetic status	F0		F1		F2		F3	
	N	%	N	%	N	%	N	%
Yes	28	29.2%	13	76.5%	5	83.3%	2	100%
No	68	70.8%	4	23.5%	1	16.7%	0	0
Total	96		17		6		2	

Table 12: Mean fasting blood sugar and fibrosis association

	F0		F1		F2		F3		F value	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Fasting glucose (mg/dl)	120.19	15.34	132.76	15.08	130.83	14.59	144.00	22.63	4.9	<0.05

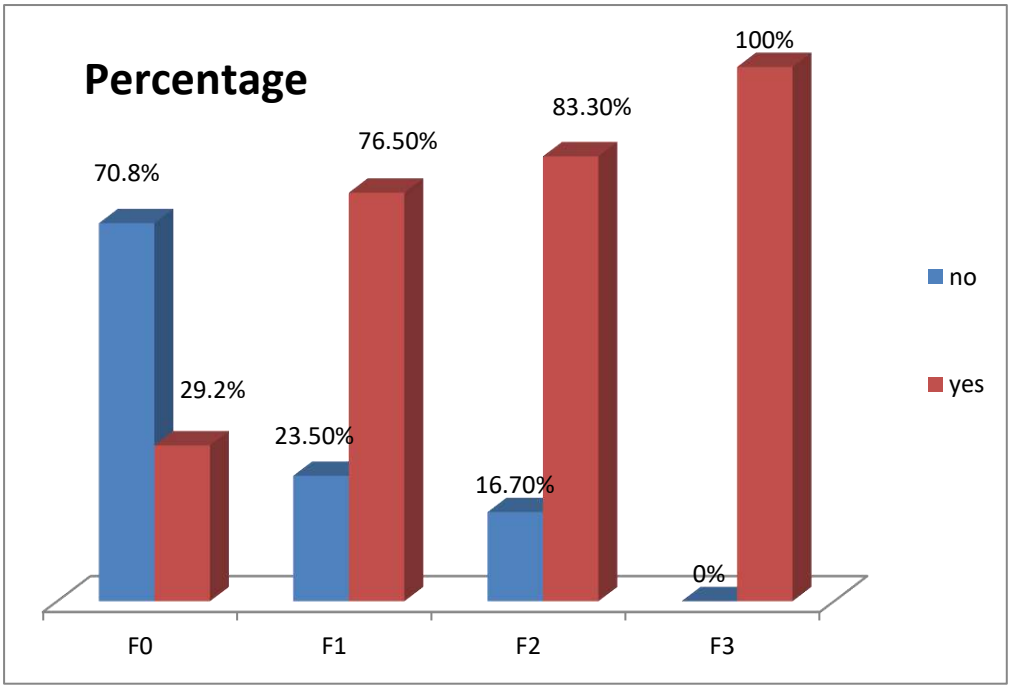

Figure 13: Diabetic status among different fibrosis group.

Association of fibrosis with hypertriglyceridemia

In patients with no fibrosis, 44.8 % patients had hypertriglyceridemia.

In patients with fibrosis 21 out of 25 (84%) patients had hypertriglyceridemia with increasing association with severity of fibrosis. 82.4 % patients with F1 grade, 83.3 % patients with F2 grade and all patients with F3 grade had hypertriglyceridemia.

There was a direct and significant association between hypertriglyceridemia and presence and severity of fibrosis (p value <0.05).

Table 13: Hypertriglyceridemia among different fibrosis grades.

Hypertriglyceridemia	F0		F1		F2		F3	
	N	%	N	%	N	%	N	%
Yes	43	44.8%	14	82.4%	5	83.3%	2	100%
No	53	55.2%	3	17.6%	1	16.7%	0	0
Total	96		17		6		2	

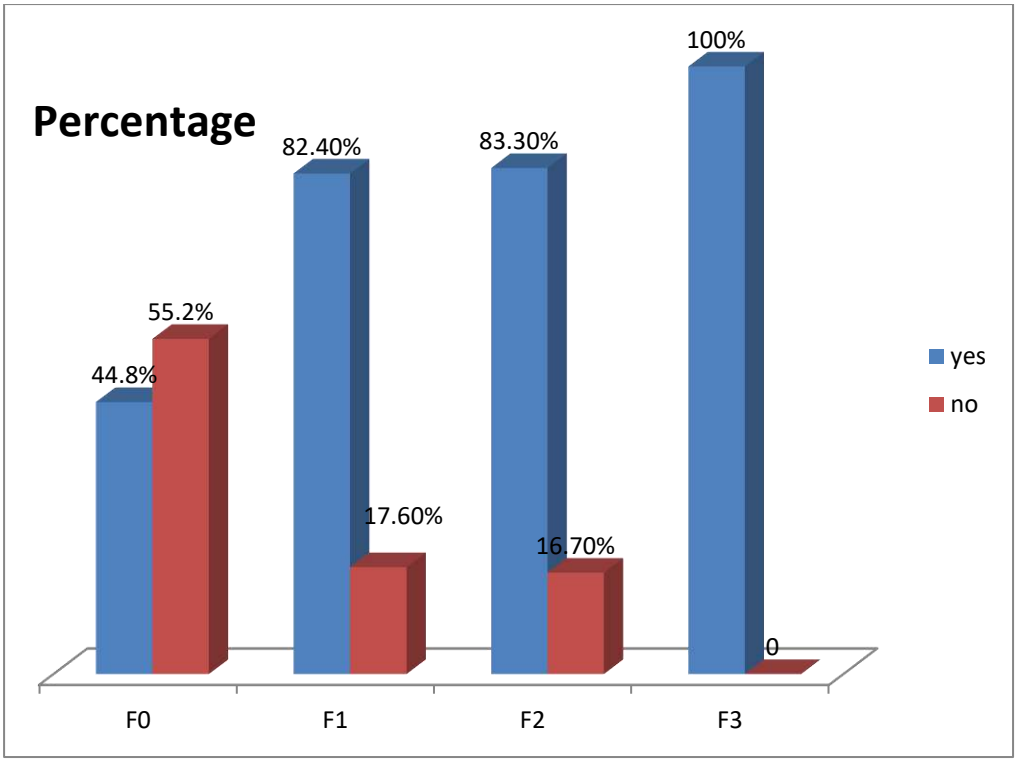

Figure 14: Hypertriglyceridemia in different fibrosis groups.

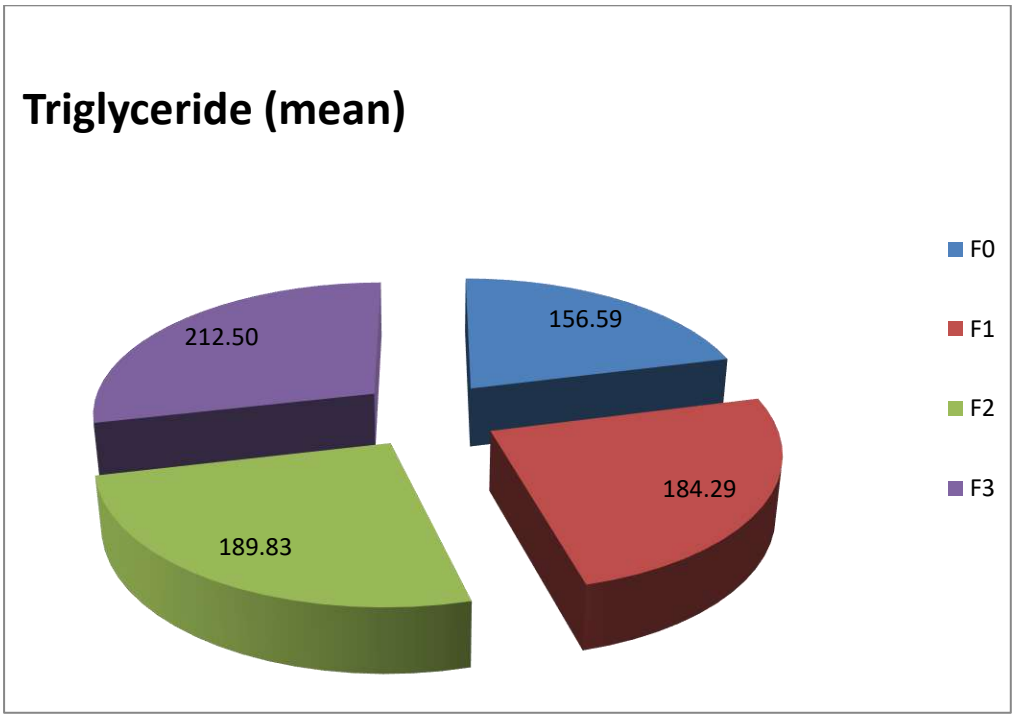

Fig 15: Mean TGs (mg/dl) levels in different fibrosis groups.

Table 14: Association of lipid levels with non-obese NAFLD

	No fibrosis (F0)		Fibrosis (F1-F3)		F Value	P Value
	Mean	SD	Mean	SD		
Total cholesterol (mg/dl)	196.5	30.8	238.8	25.7	14.9	2.5
TGs (mg/dl)	156.5	41.9	187.5	36.5	11.3	<0.05
HDL (mg/dl)	94.7	0.3	34.8	5.4	21.1	<0.05
LDL (mg/dl)	138	33	161	15	1.54	<0.05

There was significant correlation between presence and severity of fibrosis with triglyceride, HDL and LDL levels (p value <0.05).
Association between total cholesterol levels and fibrosis was found not to be significant (p value >0.05).

Table 15: Association of lipid levels with severity of fibrosis in non-obese NAFLD.

	F0		F1		F2		F3		F Value	P Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Total Cholesterol (mg/dl)	196.52	30.82	237.29	26.55	229.83	11.00	279.00	12.73	14.9	2.5
Triglyceride (mg/dl)	156.59	41.92	184.29	38.27	189.83	36.14	212.50	3.54	4.02	<0.05
HDL (mg/dl)	44.72	10.31	34.88	5.80	35.83	5.34	32.00	2.83	7.02	<0.05
LDL (mg/dl)	138.32	33.42	163.24	15.95	154.83	13.45	169.00	7.07	3.9	<0.05

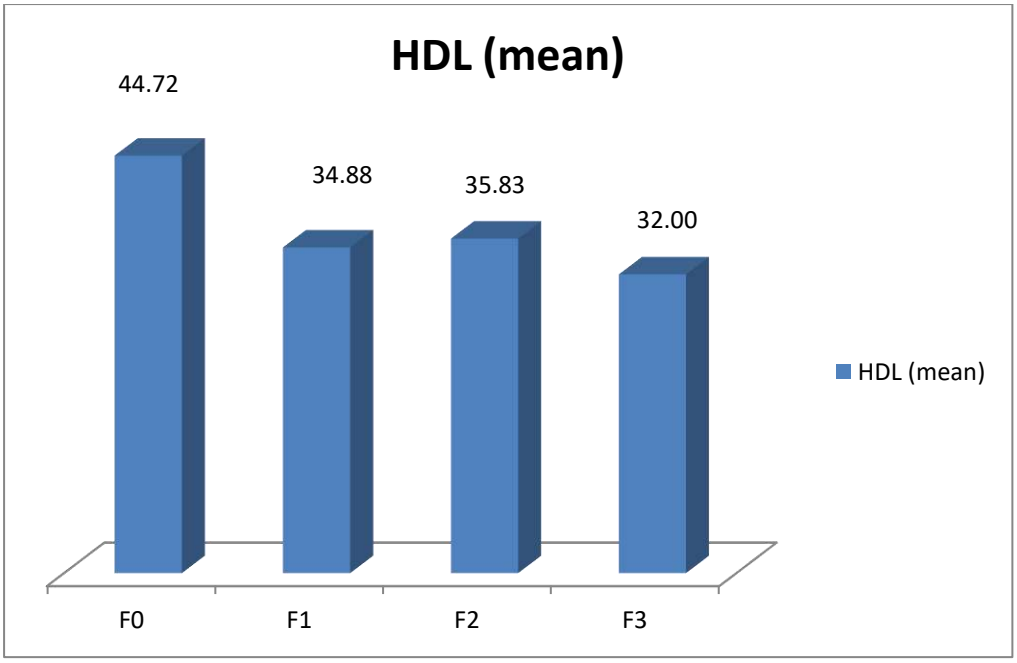

Fig 16: Mean HDL levels (mg/dl) in different fibrosis groups.

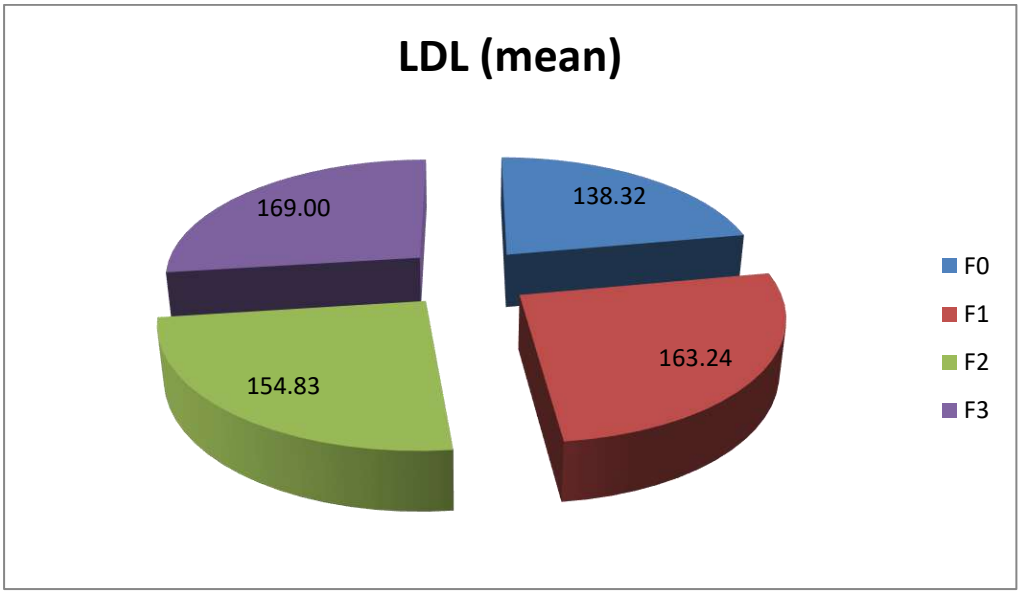

Fig 17: Mean LDL levels (mg/dl) in different fibrosis groups.

Table 16: Association of LFTs with fibrosis grade.

	F0		F1		F2		F3		F value	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
S. AST (IU/lt)	54.05	15.62	55.65	13.01	59.83	10.83	68.00	28.28	0.81	0.49
S. ALT (IU/lt)	71.30	21.01	73.18	14.96	64.17	7.39	76.50	9.19	0.35	0.78
ALP (IU/lt)	118.08	7.75	117.35	6.62	125	13.15	117	7.07	1.55	0.2

There was no statistically significant association between elevated Liver enzymes levels and grade of fibrosis in this study.

DISCUSSION

In our study all non-obese NAFLD patients attending the OPD and admitted in Gastroenterology department of DMCH within one year (March 2018 to March 2019) were enrolled.

Total number of patients in our study were 121.

In our study age of patients ranged from 30 to 63 years with 28 (23.1%) less than 40 years of age; 62 (51.2%) between 41-50 years of age and 31 (25.6 %) were aged >50 years. Average age of lean NAFLD individuals in various studies ranged from 38-60 years. Das et al[15] in their study stated that peak prevalence of non alcoholic fatty liver in lean subjects was in 4th decade. Majority of patients in our study were between 41-50 years of age (51.2%).

In our study majority, 61.2% patients were males (74/121) and 38.8% (47/121) patients were females. Slight male prepondence has been found in majority of lean/ non-obese NAFLD studies. Maximum number of patients in our study were also males(61.2%).

Among all the patients in our study, 44/121 (36.4%) were hypertensive. In their studies Feug et al[21], Kwon et al[43], Wei et al[52] showed association of hypertension with lean/ non-obese NAFLD. In study by Alam et al[18], 26.2 % non-obese NAFLD patients had hypertension. Prevalence of hypertension in lean/ non-obese NAFLD subjects ranged from 15-43% in various studies, this is comparable to prevalence of hypertension (36.4%) in non-obese NAFLD subjects in our study.

Among all the patients in our study 48/121(39.7 %) were diabetic. In study by Alam et al [18], 26.2 % non-obese NAFLD patients had diabetes. Various studies (Kim et al[19], Feug et al[21], Kwon et al[43], Das et al[15]) have shown significant association of impaired fasting blood glucose, insulin resistance and diabetes with development of NAFLD in non-obese subjects.

64/121 (52.9%) patients in our study had hypertriglyceridemia and 68/121 (56.2%) had dyslipidemia. A study by Kim et al[19] demonstrated that high triglyceride levels were significantly associated with development of NAFLD among non-obese individuals. In their study

Alam et al[18], stated a prevalence of 73.2% of hypertriglyceridemia among non-obese NAFLD. It was higher than our study, they however used cut off BMI of 25kg/m2 vs. 22.9 kg/m2 cut off used in our study. Study by Kwon et al[43] showed that lean NAFLD was associated with high TGs. In their study Kumar et al[17] found that 89% of lean NAFLD individuals were dyslipidemic.

In our study frequency of liver fibrosis i.e. grade F1 and above was 20.7 % using fibroscan i.e. 25/121 non-obese NAFLD individuals had liver fibrosis. In our study, majority (14%) patients of liver fibrosis had mild fibrosis (F1 grade) i.e., 17/121 as per fibroscan estimation. 6/121 (5%) and 2/121(1.7%) had moderate (F2) and significant (F3) fibrosis grade respectively. Various studies have stated that advanced fibrosis in non-obese NAFLD individuals is relatively low[16]. In their study of 27 lean NAFLD patients Kumar et al[17] found that 50 % of lean NAFLD had liver fibrosis on liver biopsy and 5.6 % subjects had significant fibrosis. In their study Leung et al[16], biopsied 72 non-obese NAFLD patients (BMI <25kg/m2) and found that 55.1% of them had fibrosis and 26 % had severe fibrosis on biopsy. They also did LSM by fibroscan on 17 patients of non-obese NAFLD and found 20.3 % had significant fibrosis. In their study Kwon et al[43] found that only 2.6 % of their non-obese NAFLD subjects had significant fibrosis. In our study 6.7 % individuals had >/= F2 grade fibrosis. In study by Vos et al[36] they found that 19% on non-obese NAFLD subjects (cut off BMI taken as 30 kg/m2) had >/= F2 grade fibrosis. In another study by Alam et al[18], this prevalence was 20% (BMI cut off 25 kg/m^2). Our study had lower frequency of fibrosis as compared to these studies; however, BMI cut off in most of these studies was more than 25kg/m^2. Many of the previous studies had used liver biopsy to diagnose fibrosis. Also, our study was limited to one year time period and most of the previous studies included follow up of non-obese NAFLD patients contributing to increased fibrosis prevalence.

Mean kPa value was 5.2 +/-0.79 in all non-obese individual in our study. Mean kPa values in non-obese NAFLD in various studies was 5+/-1.6 kPa in study by Margriti et al[72], 4.6 +/- 1.5 kPa in study by Kwon et

al[43], 5.9 kPa in study by Kumar et al[17], 6.3 kPa in study by Leung et al[16], which were comparable to our study.

In our study among all non-obese NAFLD patients who had fibrosis; 14/25 (56%) were males and 11/25 (44%) were females.

In our study; there was an increasing age trend with increase in severity of fibrosis which was statistically significant (p value <0.05). Mean age being 44.6 +/- 5.4 years in those having F1 fibrosis; 51.6+/-4.6 years in those with F2 fibrosis and 61.5 +/-1.2 years in those with F3 grade.

In our study of all patients with fibrosis; 20/25 (80%) had diabetes. Our study showed significant association between diabetic status and presence and severity of fibrosis (p value<0.05). 76.5 % patients in F1 grade, 83.3 % patients in F2 grade and all patients in F3 grade had diabetes. There was a statistically significant association between fasting blood glucose levels and severity of fibrosis. Although many studies have shown significant association of NAFLD in non-obese individuals with diabetic status, impaired fasting blood glucose. There is limited data for association of fasting blood glucose levels and diabetic status with severity of fibrosis in non-obese NAFLD individuals.

In our study 21/25 (84%) of all having fibrosis had hypertriglyceridemia. Our study also showed an increasing association of hypertriglyceridemia with severity of fibrosis- 44.8% individuals with no fibrosis had hypertriglyceridemia; 82.4% patients with F1 grade fibrosis and 83.3% patients with F2 grade fibrosis had hypertriglyceridemia. All patients with F3 grade fibrosis had hypertriglyceridemia. Our study showed a direct and significant association between hypertriglyceridemia and presence and severity of fibrosis (p value<0.05). Mean values of TGs (mg/dl) being 156.5+/-41 in no fibrosis group, 184.2 +/-38.2 in F1 grade, 189+/-36 in F2 grade and 212.5 +/-3.5 in F3 grade patients.

There also was a statistically significant association between LDL and HDL levels with presence and grade of fibrosis (p value<0.05).

Mean values of LDL (mg/dl) being 138.3+/- 33.4 in no fibrosis group, 163.2 +/-15.9 in F1 grade, 154.8+/- 13 in F2 grade and 169.5 +/-7 in F3 grade patients.

Mean values of HDL (mg/dl) being 44.7.3+/-10.3 in no fibrosis group, 34.8 +/-5.8 in F1 grade, 35.8+/- 5.3 in F2 grade and 32 +/-2.8 in F3 grade patients.

There was no statistically significant association between total cholesterol values and fibrosis in our study.

Many previous studies have shown a direct and strong association of development and severity of fibrosis in non-obese NAFLD individuals with dyslipidemias.

Ampuero J et al[69] stated that there is a strong association of altered LDL/HDL ratio with severity of fibrosis in lean NAFLD patients. Lee SY et al[75] in study of non-obese non diabetic NAFLD patients have found that hypertriglyceridemia was linked to development of fibrosis in NAFLD patients. In their study Kumar et al[17] and Leung at el[16] have found that elevated serum TGs levels were independently associated with higher NAFLD score and fibrosis.

Although there are studies that have linked elevated ALT levels to indication and prediction of liver fibrosis (Das et al[15]). There was no statistically significant association between elevated Liver enzymes levels and presence or severity of fibrosis in our study.

Studies on association between metabolic status of patients and severity of fibrosis in obese NAFLD patients are not many but they have yielded important results. In our study frequency of fibrosis among non-obese NAFLD individuals was 20.2% (25/121). Majority patients of liver fibrosis had mild fibrosis (F1 grade) i.e. 17/121 (14%) as per fibroscan estimation. 6/121 (5%) had moderate (F2 Grade) fibrosis. Significant fibrosis (F3 grade) was seen in 2/121(1.7%).

Although frequency of fibrosis and significant fibrosis was lower in our study as compared to most of the previous studies, this could be due to difference in BMI cut off and method of detecting fibrosis (biopsy vs fibroscan). Our study however did show a strong association of diabetic status and dyslipidemia (elevated TGs, elevated LDL and low HDL levels) with development and severity of fibrosis in non-obese NAFLD individuals.

Although our study looks promising but it still has few limitations. The major limitation is taking USG as diagnostic modality for NAFLD and transient elastography as reference point for grading of fibrosis. Although USG and TE have good overall accuracy for diagnosis of fatty liver and diagnosis of fibrosis but liver biopsy is still considered to be the gold standard for diagnosis of both. Other limitation was hospital based selection of patients and no long term follow up of the patients. Further studies will be needed for assessment of fibrosis in non-obese NAFLD individuals which are based on general population.

SUMMARY

Our study enrolled all non-obese NAFLD patients attending OPD and being admitted in gastro department of DMC and Hospital within 1 year (March 2018 to March2019). Total number of patients in our study was 121.

1. Average age of patients in our study ranged from 30-63 years. Majority of patients were between 41-50 years of age (51.2%). Most of the patients in our study were males (61.2%).
2. Frequency of fibrosis (by fibroscan) in our study of non-obese NAFLD was 20.7 % (25/121). 14% patients had mild (F1) fibrosis, 5% had moderate (F2) and 1.7% had significant (F3) fibrosis.
3. Mean kPa value was 5.2+/-0.79 in our study.
4. 80% of patients with fibrosis in our study were diabetic. Our study showed a direct and significant association between diabetic status and presence and severity of fibrosis (p value<0.05).
5. In our study 21/25 (84%) of patients with fibrosis had hypertriglyceridemia. There was a direct and significant association between hypertriglyceridemia and presence and severity of fibrosis (p value<0.05). Mean values of TGs (mg/dl) being 156.5+/-41 in no fibrosis group, 184.2 +/-38.2 in F1 grade, 189+/-36 in F2 grade and 212.5 +/-3.5 in F3 grade patients.
6. There also was a statistically significant association between LDL and HDL levels with presence and severity of fibrosis (p value<0.05).
7. There was no statistically significant association between total cholesterol values and fibrosis in our study
8. There was no statistically significant association between elevated Liver enzymes levels and presence or severity of fibrosis in this study.

CONCLUSION

In conclusion, frequency of fibrosis in non-obese NAFLD patients in our study was 20.7%, with significant fibrosis (>/=F3) seen in 1.7%. Although there are limitations in our study, statistically significant association between diabetic status and abnormal lipid profile with presence and severity of fibrosis in non-obese NAFLD patients was established in our study.

At present there are limited studies on non-obese NAFLD; prevalence of fibrosis and metabolic abnormalities in non-obese NAFLD.

As the burden and clinical impact of NAFLD is increasing in non-obese individuals especially in Asian countries, further large scale studies are needed for assessment of fibrosis in non-obese NAFLD and its association with various components of metabolic syndrome.

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Key to Master Chart

AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
BMI	Body Mass Index
HB	Hemoglobin
HCT	Hematocrit
HDL	High Density Lipoprotein
HTN	Hypertension
kPa	kilo Pascal
LDL	Low Density Lipoprotein
USG	Ultrasonography

Sr. No	MRD No	GENDER	AGE	BMI	BP	HTN	HB	HCT	Fasting glucose	Fasting insulin	DIABETES	Total Cholesterol	Triglyceride	HDL	LDL-c	DYSLIPIDEMIA	HYPERTRIGLYCERIDEMIA	S. Bilirubin (Total)	S. Bilirubin (Direct)	S. Alkaline Phosphatase	S. AST	S. ALT	S. Total Protein	S. Albumin	S. Urea	S. Creatinine	S. Sodium	S. Potassium	Thyroid stimulating hormone (TSH)	USG (FATTY LIVER GRADE)	FIBROSCAN (Kpa)	FIBROSIS GRADE
1	449274	M	40	22	130/80	yes, onmed	11	36	102	N/A	no	190	160	50	60	yes	yes	1.2	0.5	102	30	32	5.2	3.2	25	0.5	132	4.2	2.2	I	5.7	F0
2	449294	M	51	22.5	120/70	no	12	39	134	N/A	yes	210	170	42	60	yes	yes	1.2	0.7	136	25	27	5.1	3	20	0.9	141	4.5	3.5	II	5.8	F0
3	167344	F	50	22.8	140/90	yes	13.2	39	145	30	yes	230	210	35	160	yes	yes	1.3	0.4	135	62	74	5.9	3.5	22	0.7	135	3.9	5.9	III	6.2	F2
4	56924	F	49	21	126/74	no	10	36	104	N/A	yes,on med	226	185	30	168	yes	yes	1.1	0.5	120	55	64	4.4	2.9	18	0.3	135	3.8	11.22	III	6.4	F2
5	450425	M	32	22.5	120/80	no	13	37	108	N/A	no	170	140	52	60	no	no	1.7	0.6	126	26	33	5.1	3	26	0.7	132	3.8	0.414	I	4.5	F0
6	451023	F	49	22.8	128/78	no	11	35	102	N/A	no	160	120	42	66	no	no	1.4	0.4	110	19	25	4.8	2.8	24	0.5	141	4	3.6	I	3.4	F0
7	449060	F	46	22.8	130/82	yes, on med	12	36	140	32	yes	235	184	35	150	yes	yes	1.6	0.3	145	52	62	5.2	2.9	36	1.1	140	4.2	3.22	III	6.3	F2
8	436544	M	36	22.8	126/74	no	14	38	110	N/A	no	180	126	52	70	no	no	1.2	0.5	110	30	42	5.4	3.2	26	0.8	132	4.3	2.34	I	4	F0
9	456710	M	45	22.8	134/84	yes, on med	13	36	124	N/A	no	170	142	50	76	no	no	1.1	0.3	120	34	36	4.8	2.9	40	1.1	128	3.9	1.36	I	4.9	F0
10	446796	F	55	22.7	132/76	yes, on med	11.4	39	120	N/A	no	210	149	44	130	yes	no	1.2	0.4	126	47	52	4.6	2.7	39	1.1	141	4.8	2.38	II	6.5	F2
11	462221	F	34	21	140/90	yes	10	38	115	N/A	no	220	170	39	151	yes	yes	1	0.3	145	55	57	5.2	3	35	0.9	136	4.5	5.56	III	5.3	F0
12	462414	M	36	22.8	128/80	no	14	38	110	N/A	no	180	174	52	140	yes	yes	1.2	0.4	128	34	39	5.4	3.4	36	1	138	4.8	3.66	II	4.4	F0
13	46622	M	54	22.8	136/86	yes	12	36	124	N/A	yes, on med	184	166	48	148	yes	yes	1.3	0.5	130	38	42	4.8	2.9	32	1.2	132	4.4	1.65	II	4.1	F0
14	179594	F	60	22.4	138/90	yes	11	37	126	N/A	yes, on med	186	170	46	138	yes	yes	1.1	0.3	126	36	44	4.8	2.8	34	1.1	130	4.2	2.08	II	4.7	F0
15	56034	F	40	22.6	128/78	no	11.5	38	142	N/A	yes	220	161	35	162	yes	yes	1.4	0.6	130	42	46	4.9	3	32	1.1	136	4	3.78	III	6	F1
16	341389	F	46	22.8	126/70	no	12	37	120	N/A	yes, on med	170	150	46	110	no	no	1.1	0.5	124	32	36	5	3.5	30	0.9	132	4.2	4.12	I	4.5	F0
17	482245	M	39	22.7	128/72	no	13	38	118	N/A	no	160	148	54	150	no	no	1.4	0.7	130	35	40	5.6	3.9	36	1.1	128	4.1	1.08	II	5.1	F0
18	365262	M	51	22.8	140/90	yes	12	39	105	N/A	no	240	210	50	152	yes	yes	1.1	0.3	110	47	52	5	3.1	32	0.8	142	4.2	2.38	I	4	F0
19	490668	M	47	21	130/82	no	11	38	98	N/A	no	170	120	46	72	no	no	1	0.3	124	24	32	5.2	3.6	42	0.9	132	4.9	1.87	I	5.6	F0
20	106794	M	51	22.8	140/90	yes	13.4	42	130	N/A	yes	240	250	40	160	yes	yes	1.1	0.3	112	77	64	5.3	2.6	25	0.8	126	3.6	2.4	III	6.4	F2
21	152363	F	46	22.7	130/84	no	12.2	36	135	N/A	yes	202	230	32	164	yes	yes	1.2	0.3	120	80	92	5.2	2.7	26	1	123	3.7	2.5	III	4.4	F0
22	67112	M	50	22.8	142/90	yes	13.6	44	140	25	yes	250	280	42	166	yes	yes	1.1	0.4	110	84	66	5	2.6	28	1.2	128	3.7	2.6	II	4.8	F0
23	206594	F	37	22.8	126/70	no	11.4	37	120	N/A	no	180	110	44	78	no	no	1.1	0.3	115	44	77	4.8	3.5	30	1	122	4.2	4.3	I	4.8	F0
24	489473	F	46	22.6	130/80	no	11	38	130	16	yes, on med	188	126	36	175	no	no	1.4	0.7	116	45	73	4.9	3.4	32	1.1	124	4.1	4	II	5.3	F0
25	488266	M	47	22.7	124/74	no	13.8	42	115	8	no	190	148	52	108	no	no	1.3	0.5	118	50	77	5.1	3.3	35	0.9	126	4.4	3.8	I	5.2	F0
26	489366	M	48	22.8	126/80	no	14	45	130	N/A	yes	242	300	40	178	yes	yes	1.2	0.4	120	62	79	5.5	2.6	36	0.7	130	4.4	3.9	I	5.5	F0
27	437271	M	60	22.4	150/90	yes, on med	14.2	46	128	N/A	yes, on med	270	210	30	164	yes	yes	1.2	0.3	122	48	83	4.7	3	32	1.2	134	4.6	2.6	III	8.1	F3
28	340993	M	36	22.1	118/72	no	13.6	42	100	14	no	180	144	50	110	no	no	1.4	0.5	124	44	63	4.8	3.1	30	0.6	132	3.7	2.5	I	4.9	F0
29	276075	F	50	22.6	110/70	no	11	35	112	12	no	178	138	38	170	no	no	1.3	0.4	108	64	75	4.9	3	38	1.1	136	3.9	2.9	I	5.2	F0
30	486057	M	51	22.8	126/70	no	13.9	48	124	11	no	176	130	52	108	no	no	1.5	0.6	110	97	90	4.9	3.5	27	1	137	4	3	I	5.2	F0
31	441472	F	63	22.8	130/80	yes, on mes	11.2	39	160	N/A	yes	288	215	34	174	yes	yes	1.2	0.3	112	88	70	5.1	3.1	28	1.2	138	4.1	3.2	III	8.2	F3
32	483146	M	43	22.4	114/70	no	14	43	118	N/A	no	188	132	44	180	no	no	1.3	0.4	126	74	84	5.3	3.3	30	0.8	125	4	3.3	I	5.5	F0
33	487945	M	45	22.4	100/68	no	14	45	120	N/A	no	190	130	46	172	no	no	1.6	0.5	106	60	67	5.2	3.2	34	0.9	127	4	3.4	I	5.6	F0
34	29458	M	53	22.5	142/92	yes	14.5	46	150	29	yes	212	230	42	188	yes	yes	1.4	0.3	122	90	54	5	3.4	35	0.6	125	4.8	3.5	II	5.8	F0
35	483814	F	43	22.5	110/70	no	12	37	112	N/A	no	194	126	38	184	no	no	1.3	0.3	120	93	70	4.8	3.3	36	1.1	126	4.7	12.2	I	4.5	F0
36	27486	F	54	22.6	126/80	no	12.6	40	110	13	no	182	144	40	98	no	no	1.2	0.3	118	80	84	4.7	3	37	1.2	138	4.6	13.6	I	4.8	F0
37	487610	M	48	22.8	124/70	no	13.7	40	124	N/A	no	194	240	40	90	yes	yes	1.2	0.3	116	45	53	5.5	2.9	32	1	134	4.4	3.6	I	4.4	F0
38	74456	M	53	22.8	160/90	yes	14.7	42	156	N/A	yes	200	260	42	168	yes	yes	1.1	0.3	110	48	52	5.6	3	26	0.9	136	4.3	3.7	II	4.5	F0
39	165382	F	48	22.4	132/80	yes, on med	12.5	38	108	20	no	186	126	38	171	no	no	1.4	0.4	112	36	66	5.4	3.2	27	0.8	127	4.3	12.9	II	5.5	F0
40	480395	F	40	22.7	130/80	yes, on med	11.3	42	132	22	yes	186	128	38	178	no	no	1.4	0.5	114	44	65	5.6	3.1	25	0.8	128	4.2	14.3	III	6	F1
41	480460	M	44	22.4	120/80	no	14.2	44	120	10	no	188	118	52	100	no	no	1.1	0.3	106	47	70	5.4	3.2	28	0.9	129	3.9	4	I	5.2	F0
42	123222	F	52	22.8	146/88	yes	12	45	124	N/A	no	200	275	32	180	yes	yes	1.2	0.3	108	43	46	5.2	3.3	30	0.8	130	3.8	4.1	II	5.2	F0
43	473717	M	38	21	118/82	no	14.2	45	122	N/A	no	180	132	50	100	no	no	1.1	0.3	112	52	55	4.9	2.9	31	1.1	123	4.1	4.2	I	5.2	F0
44	479658	M	36	21.9	110/70	no	13.9	48	148	N/A	yes	206	280	44	186	yes	yes	1.3	0.4	115	56	59	4.8	2.8	33	1.2	134	4.4	3.8	II	6	F1
45	270705	M	41	22.3	120/80	no	14.4	47	106	N/A	no	180	140	52	110	no	no	1.3	0.4	116	45	73	5.1	3.3	37	1	138	4.6	3.9	I	5.9	F0
46	306405	F	35	22.2	126/72	no	10.8	37	110	N/A	no	180	130	38	190	no	no	1.5	0.5	110	49	84	5.2	3.4	38	1	139	4	12.2	I	5.9	F0
47	243018	M	59	22.7	134/74	yes, on med	13.8	40	180	N/A	yes	268	250	42	174	yes	yes	1.1	0.3	107	40	67	5.6	3.5	34	0.9	137	4.4	3	II	6	F1
48	406343	F	49	22.6	130/80	no	12	44	112	N/A	no	200	162	42	173	yes	yes	1.4	0.3	106	57	102	5.5	2.8	35	0.8	135	4.3	3.1	I	5.2	F0
49	480913	M	43	22.6	126/80	no	13.9	43	200	27	yes	225	275	40	160	yes	yes	1.2	0.3	112	61	79	4.8	2.7	26	0.9	129	4	3.2	II	4.9	F0
50	328520	M	44	22.7	124/72	no	14.3	45	120	N/A	no	176	132	52	120	no	no	1.1	0.4	124	67	48	4.9	2.7	27	0.7	130	4.1	3.3	I	4.8	F0
51	231140	M	47	22.1	140/95	yes	14	41	130	22	yes, on med	250	159	29	166	yes	yes	1.3	0.5	108	42	66	5.1	3.3	36	0.6	125	3.7	3.2	II	6	F1
52	174258	M	37	21.9	128/72	no	14.2	42	122	10	no	220	140	28	156	yes	no	1.4	0.4	110	48	65	5.5	3.5	34	1	134	3.9	3.3	II	5.3	F0
53	481599	M	59	22.7	120/80	no	13.8	42	120	N/A	no	160	120	35	155	no	no	1.2	0.5	112	54	59	5.3	3.2	35	1	125	4.3	3.4	I	5.4	F0
54	170371	F	38	22.6	110/70	no	12	38	110	N/A	no	140	130	42	154	no	no	1.2	0.3	112	56	70	4.6	3	28	1.1	127	4.4	13.3	I	5.1	F0
55	481691	M	45	22.4	160/90	yes	14	44	111	N/A	no	289	200	36	155	yes	yes	1.2	0.4	115	65	77	5	3	27	1	126	4.1	3	II	5	F0
56	481510	F	43	22.6	155/89	yes	12	37	138	28	yes	270	190	27	160	yes	yes	1.1	0.5	117	68	73	4.4	3	29	0.9	128	4	1.1	III	6	F1
57	482065	F	44	22.8	110/70	no	11.8	38	120	N/A	no	180	126	44	154	no	no	1.4	0.4	118	74	71	4.6	3.1	38	0.9	126	4.5	1.5	I	5.5	F0
58	360862	M	44	22.8	120/80	no	14.5	44	123	N/A	no	159	110	44	160	no	no	1.5	0.3	120	49	78	5.1	3.3	32	0.7	134	3.4	2.2	I	5.2	F0
59	263101	F	51	22.8	110/75	no	11.5	38	109	N/A	no	220	160	38	159	yes	yes	1.3	0.2	128	44	80	4.7	2.9	25	0.8	135	3.5	1.9	II	5.3	F0
60	478622	F	53	22.8	148/90	yes	12.5	40	132	N/A	yes	260	170	29	179	yes	yes	1.2	0.4	125	43	99	4.8	2.8	27	1	133	4.5	2.5	II	5.3	F0
61	476651	M	44	22.4	128/72	no	14.4	43	108	N/A	no	276	166	32	151	yes	yes	1.3	0.4	120	45	109	5.2	3.3	28	0.8	136	3.9	3	I	4.9	F0
62	401236	M	38	22.2	120/70	no	14.5	46	105	N/A	no	210	155	35	142	yes	yes	1.4	0.4	116	54	98	5.4	3.1	28	1	135	3.8	3.5	I	4.8	F0
63	471579	F	45	22.1	120/80	no	12	39	120	N/A	no	209	160	66	122	yes	yes	1.5	0.3	109	66	94	4.9	2.9	29	0.9	125	4.1	3.3	I	4.3	F0
64	476597	M	42	22	110/70	no	13.5	44	112	N/A	no	190	106	35	142	no	no	1.3	0.3	110	65	108	5.2	3.2	31	1.1	127	4.6	2.7	I	4.4	F0

Sr. No	MRD No	GENDER	AGE	BMI	BP	HTN	HB	HCT	Fasting glucose	Fasting insulin	DIABETES	Total Cholesterol	Triglyceride	HDL	LDL-c	DYSLIPIDEMIA	HYPERTRIGLYCERIDEMIA	S. Bilirubin (Total)	S. Bilirubin (Direct)	S. Alkaline Phosphatase	S. AST	S. ALT	S. Total Protein	S. Albumin	S. Urea	S. Creatinine	S. Sodium	S. Potassium	Thyroid stimulating hormone (TSH)	USG (FATTY LIVER GRADE)	FIBROSCAN (Kpa)	FIBROSIS GRADE
65	476614	M	46	22.8	145/95	yes	13.4	40	120	N/A	no	288	203	29	166	yes	yes	1.4	0.4	110	80	110	5.3	3	33	1.1	128	4.3	2.7	II	6	F1
66	118300	M	45	22.7	155/90	yes	13.2	41	125	N/A	yes, on med	268	210	33	134	yes	yes	1.5	0.5	115	76	76	5	3	36	1.1	129	4.2	3.4	II	6	F1
67	436882	F	40	22.3	120/80	no	11	35	160	29	yes	220	188	36	138	yes	yes	1.1	0.3	117	43	77	4.1	2.4	37	0.8	130	3.8	3.3	I	5	F0
68	478541	M	36	21.8	130/70	no	14	46	136	22	yes	256	175	32	140	yes	yes	1.2	0.3	111	45	80	5.2	3.2	34	0.8	132	3.9	4	II	5.7	F0
69	118297	F	44	22.5	110/80	no	10.8	36	140	N/A	yes	200	180	56	128	yes	yes	1.3	0.3	110	75	89	4	3	34	0.8	125	4.1	3.3	I	5.8	F0
70	33177	M	48	22.5	120/80	yes, on med	13.1	44	150	N/A	yes	223	146	37	139	yes	no	1.3	0.3	119	45	92	5.1	3	35	0.8	133	4	3	III	5.9	F0
71	478727	M	52	22.8	140/95	yes	14	40	144	32	yes	250	175	38	147	yes	yes	1.4	0.4	116	54	95	5.2	3.5	32	0.9	136	4.4	3	III	5.4	F0
72	407315	M	42	22.4	120/80	no	13.8	41	110	N/A	no	148	110	69	112	no	no	1.5	0.2	126	55	99	4.9	3	30	0.7	138	4.3	2	I	4.2	F0
73	477749	M	43	22.8	110/80	no	13.7	43	109	N/A	no	158	109	65	129	no	no	1.1	0.3	124	65	96	4.8	3.3	29	0.6	130	4.2	2.9	I	3.2	F0
74	290521	M	46	22.8	150/95	yes	13.9	46	120	N/A	yes,on med	246	148	32	137	yes	no	1.5	0.2	127	46	90	5.3	2.9	28	1.2	129	3.9	3.2	III	6	F1
75	149915	F	47	22.8	148/92	yes	12.1	37	129	N/A	yes	230	180	30	166	yes	yes	1.2	0.2	110	44	80	4.1	2.7	26	1	127	3.7	3	II	5.8	F0
76	137456	F	48	22.3	120/80	no	12.8	36	110	N/A	no	160	110	68	123	no	no	1.3	0.3	116	59	82	4	2.6	33	0.9	130	3.6	3.1	I	4.2	F0
77	232760	M	40	21.7	112/80	no	14	42	101	N/A	no	178	102	66	126	no	no	1.3	0.4	117	62	60	5.2	2.9	32	0.6	131	4.4	1.8	I	3.9	F0
78	174676	M	42	22.5	120/70	no	14	41	104	N/A	no	180	104	56	120	no	no	1.6	0.4	126	62	64	5.5	3.4	33	0.7	136	4.2	1.6	I	4	F0
79	399744	M	48	22.6	148/90	yes	14.5	40	124	N/A	yes, on med	240	148	37	159	yes	no	1.5	0.5	116	64	65	5	3.3	26	1.1	137	3.6	1.8	II	6	F1
80	475118	M	59	22.8	150/98	yes	13.9	45	138	27	yes	238	152	31	161	yes	yes	1.6	0.2	112	66	69	5	3.2	32	1.2	133	3.9	3	III	6.4	F2
81	479094	F	39	22	110/70	no	11	39	110	N/A	no	159	102	50	122	no	no	1.4	0.3	113	70	70	4.3	2.8	31	0.7	126	4.4	12.6	II	4.4	F0
82	476080	M	44	22.2	100/60	no	14.4	44	103	N/A	no	160	110	39	120	no	no	1.3	0.4	110	72	72	4	2.7	30	0.8	128	4	3	I	4	F0
83	397641	F	45	22.8	130/70	no	11	38	130	17	yes, on med	220	180	30	166	yes	yes	1.1	0.2	112	55	75	4.4	2.6	25	1.1	128	3.6	10.9	III	6	F1
84	430229	F	57	22.1	120/70	no	12	39	120	N/A	no	280	190	32	159	yes	yes	1.3	0.2	114	57	74	4.6	2.8	26	1	132	4.2	2.3	II	4.9	F0
85	476206	M	30	22.4	135/80	yes	13.6	42	110	12	no	180	140	66	170	no	no	1.2	0.3	110	58	89	5	3.3	33	0.9	133	4.4	2.2	I	3.8	F0
86	140903	F	49	22.5	150/90	yes	11	35	109	N/A	no	245	179	30	177	yes	yes	1.3	0.4	120	65	88	4.3	3.2	32	1	137	4.8	2.7	II	5.5	F0
87	324207	M	39	22.7	138/90	yes	15	41	120	N/A	no	230	188	36	168	yes	yes	1.2	0.3	123	54	80	5.2	3.3	30	1.2	139	3.6	1.8	II	6	F1
88	112091	M	55	22.8	120/80	no	14	44	135	16	yes, on med	170	120	50	129	no	no	1.2	0.2	125	53	93	5	3.5	28	0.8	126	3.6	1.6	I	5.4	F0
89	476602	M	40	22.8	110/70	no	14.5	43	138	19	yes, on med	238	154	38	169	yes	yes	1.1	0.3	117	45	95	5.3	3.3	27	1	128	4.8	3.3	II	6	F1
90	339256	F	55	22.6	148/98	yes	13	46	122	N/A	no	204	169	39	156	yes	yes	1.4	0.5	118	42	94	4.3	2.9	25	0.8	129	4.4	2.7	I	5.2	F0
91	476621	F	44	22.8	138/92	yes	12	37	118	N/A	no	210	166	34	180	yes	yes	1.2	0.4	124	44	58	4.4	3.6	24	1.2	132	4.3	2.5	II	6	F1
92	253873	M	49	22.7	140/90	yes	14	36	124	N/A	no	190	143	58	120	no	no	1.3	0.3	129	49	68	5.2	3.5	27	0.9	133	4.2	3.6	II	5.1	F0
93	476327	M	60	22.6	130/89	yes	13.8	35	138	21	yes	178	127	56	126	no	no	1.1	0.2	125	59	50	5.2	3.6	29	0.6	136	4.1	3.8	II	5.2	F0
94	152694	M	35	22.4	120/80	no	14.4	38	112	N/A	no	169	138	55	119	no	no	1.5	0.3	112	69	54	5.1	3.5	30	0.6	137	4	4	I	4.8	F0
95	388012	M	40	22.5	110/70	no	14.3	32	110	N/A	no	170	135	49	129	no	no	1.4	0.4	110	67	66	5.4	2.9	32	0.7	132	3.8	3	I	4.9	F0
96	467171	M	43	22.7	120/80	no	14.8	39	109	N/A	no	180	129	50	130	no	no	1.3	0.2	116	65	60	5.2	2.5	34	0.7	131	3.9	2.2	I	5	F0
97	234592	M	49	22.2	120/70	no	13.9	37	110	N/A	no	210	168	32	166	yes	yes	1.2	0.3	123	64	69	4.9	2.6	27	0.8	130	3.7	2.8	I	5	F0
98	36508	F	50	22.8	110/70	no	13	40	130	N/A	yes	198	160	33	178	yes	yes	1.1	0.5	127	66	77	4.3	2.9	25	0.9	136	4.2	2.2	II	5.1	F0
99	161970	F	42	22.7	127/82	no	12	42	122	N/A	no	218	170	48	132	yes	yes	1.1	0.5	125	74	70	4.2	3	28	1.1	128	4.7	2.1	II	6	F1
100	74316	F	43	22.4	128/80	no	11	45	120	N/A	yes, on med	187	145	49	129	no	no	1.3	0.3	127	70	73	4.1	3.1	30	1	126	4.7	11.2	II	5.2	F0
101	398472	M	52	22.8	130/80	no	14.4	33	130	27	yes	230	200	31	158	yes	yes	1.3	0.2	120	62	74	5	3	31	1.1	129	4.9	1.6	III	6	F1
102	473041	M	47	22.8	139/89	yes	14.6	35	140	20	yes	246	198	30	180	yes	yes	1.4	0.3	115	54	75	5.4	3.4	34	1.1	132	4.8	1.7	II	6	F1
103	311654	M	58	22.1	130/80	no	13.9	45	112	N/A	no	229	180	34	184	yes	yes	0.2	0.4	112	52	89	5.2	3.5	33	0.7	133	4.4	1.8	II	4.8	F0
104	129776	F	53	22	120/85	no	13	44	106	N/A	no	234	178	33	149	yes	yes	1.2	0.2	126	58	104	4.6	3	27	0.7	137	4.1	2.7	I	4.9	F0
105	312118	M	47	22.3	110/60	no	14.7	46	120	N/A	yes, on med	185	139	59	129	no	no	1.6	0.5	124	49	105	5.5	3.4	26	0.9	136	4.2	2.5	I	5.1	F0
106	473041	M	55	22	130/80	no	14.4	43	111	N/A	no	254	199	31	139	yes	yes	1.5	0.3	120	50	98	5.3	3.3	25	1	138	3.9	3.5	II	5.2	F0
107	474029	M	56	22.1	135/85	yes	14.6	42	109	N/A	no	239	179	30	148	yes	yes	1.4	0.2	129	66	94	5.8	3.5	31	0.8	140	3.7	4	II	5.5	F0
108	222442	F	53	21.9	120/85	no	13.8	40	120	N/A	no	210	159	37	63	yes	yes	1.3	0.3	127	59	92	4.9	2.8	30	0.7	126	3.6	3.7	I	5	F0
109	228122	F	49	22.3	126/80	no	13	41	124	N/A	no	198	143	39	160	no	no	1.4	0.4	119	30	91	4.2	2.7	33	1	127	4.3	3.6	I	4.6	F0
110	301481	M	36	22.6	110/70	no	14.8	42	115	N/A	no	178	132	44	137	no	no	1.5	0.4	117	39	94	5.1	3.1	32	1	128	4.2	3.2	I	4.6	F0
111	473791	M	40	22.2	110/70	no	14	40	129	N/A	yes	169	128	49	128	no	no	1.6	0.3	118	48	58	5.2	3.4	31	1.1	129	4.4	3.3	II	4.4	F0
112	273024	M	41	22.3	120/80	no	14.4	42	119	N/A	no	159	148	50	122	no	no	1.2	0.3	112	55	55	5	3.3	30	0.8	132	4.6	3	I	4.3	F0
113	436413	F	42	22.5	120/70	no	10.7	41	108	N/A	no	228	201	31	180	yes	yes	1.2	0.3	129	56	48	4.2	2.9	26	0.8	134	4.7	2.3	I	4.2	F0
114	360822	F	48	22	120/85	no	13	44	132	N/A	yes	234	178	33	149	yes	yes	1.2	0.2	126	58	104	4.6	3	27	0.7	137	4.1	2.7	I	4.3	F0
115	96175	M	52	22.6	130/89	yes	13.8	35	140	23	yes	178	127	56	126	no	no	1.1	0.2	125	59	50	5.2	3.6	29	0.6	136	4.1	3.8	II	5	F0
116	471001	F	46	22.6	148/98	yes	13	46	122	N/A	no	204	169	39	156	yes	yes	1.4	0.5	118	42	94	4.3	2.9	25	0.8	129	4.4	2.7	I	5.5	F0
117	150355	M	30	22.4	135/80	yes	13.6	42	110	N/A	no	180	140	66	170	no	no	1.2	0.3	110	58	89	5	3.3	33	0.9	133	4.4	2.2	I	4	F0
118	119473	M	52	22.5	142/92	yes	14.5	46	144	29	yes	212	230	42	188	yes	yes	1.4	0.3	122	90	54	5	3.4	35	0.6	125	4.8	3.5	II	5.6	F0
119	131656	F	46	22.3	120/80	no	12.8	36	110	N/A	no	160	110	68	190	no	yes	1.3	0.3	116	59	82	4	2.6	33	0.9	130	3.6	3.1	I	4.2	F0
120	321619	M	44	22.4	120/80	no	14.2	44	136	22	yes	188	118	52	100	no	no	1.1	0.3	106	47	70	5.4	3.2	28	0.9	129	3.9	4	I	5.2	F0
121	466562	M	42	22.8	128/80	no	14	38	110	N/A	no	180	174	52	140	yes	yes	1.2	0.4	128	34	39	5.4	3.4	36	1	138	4.8	3.66	II	5.3	F0

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Date 19/7/19

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 31.08.2018 has approved the plan of thesis of Gaurav Maurya, a student of your college for DM Medical Gastroenterology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
To study frequency of fibrosis in non-obese individuals of nafld

Supervisor
Dr. Varun Mehta
Assoc. Prof.,
Dept. of
Gastroenterology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Ritu Dhawan Galhotra
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DMCH, Ludhiana.

The student has to submit the four copies of thesis, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

In

GASTROENTEROLOGY

OF

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

February, 2018

DR GAURAV MAURYA

DEPARTMENT OF GASTROENTEROLOGY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD
For the degree of	D.M. (Gastroenterology)
Name of the candidate	Dr. Gaurav Maurya
Supervisor	Dr. Varun Mehta, Associate Professor, Department of Gastroenterology, DMCH
Co-supervisor	Dr. Ritu Dhawan Galhotra, Associate Professor, Department of Radiodiagnosis, DMCH
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

INTRODUCTION: Nonalcoholic fatty liver disease (NAFLD) is commonly diagnosed in obese or overweight individuals. However, non-obese individuals with NAFLD are not rare but represent one significant end of the phenotypic spectrum of NAFLD. Many aspects of non-obese NAFLD need further exploration including epidemiology. This study will estimate the prevalence of fibrosis by fibroscan in non-obese individuals of NAFLD.

Aim of Study: To determine frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

Materials & Methods: All non-obese NAFLD patients of age more than 18 years (determined by BMI</=22.9kg/m 2) attending the OPD and admitted in gastroenterology department of DMCH within 1 year(march,2018 to march,2019) will be enrolled in this study. Demographic details, personal history and relevant investigations will be conducted for inclusion of subjects, all subjects will undergo fibroscan to determine degree of fibrosis.

Clinical Significance: Non-obese NAFLD is now frequently recognised in day-to-day clinical practice; however, the data on epidemiology of this entity are still scant. There are limitations in the estimations of precise prevalence of non-obese NAFLD due to absence of clinical manifestations and poor accuracy of ultrasound for mild steatosis and less sensitivity to differentiate simple steatosis from steatohepatitis. The only gold standard test for detection of this fraction is liver biopsy, which is is impractical in all patients. Fibroscan is an easy, non invasive method to evaluate liver fibrosis, needing short time to obtain results and has high accuracy in detecting level of fibrosis in NAFLD and can be a good alternative for liver biopsy

Keywords: Fibroscan, non-obese, NAFLD- non-alcoholic fatty liver disease, fibrosis.

(Signature) Candidate	(Signature) Co-Supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD"** Exist in the Department of Gastroenterology, Dayanand Medical College & Hospital and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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Place: Ludhiana, Punjab

Date: 12/4/18

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Gaurav Maurya
Department	Gastroenterology
Topic of Thesis	TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD
Likely date of appearing in DM examination	May, 2020
Date of enrollment	21, October, 2017
Name of Head of Department	Dr. Ajit Sood
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Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
	7. HOD Obst. & Gynae.
	8. Legal Expert
	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved: Yes / No

Chairperson
Research Committee
Chairperson
Research Committee

Approved: Yes / No

Chairperson
Ethics Committee
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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3	COURSE OF STUDY AND SUBJECT	DOCTORATE IN MEDICINE (D.M.) GASTROENTEROLOGY
4	DATE OF ADMISSION OF COURSE	21st OCTOBER 2017
5	TITLE OF THE TOPIC	TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Nonalcoholic fatty liver disease (NAFLD) refers to a group of conditions characterized by hepatic steatosis in the absence of significant alcohol consumption. The spectrum of NAFLD ranges from simple steatosis (hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or fibrosis) and non-alcoholic steatohepatitis - NASH. Non-alcoholic fatty liver disease (NAFLD) is fast attaining the status of being the most common liver disease throughout the world. Its prevalence is as high as 20-30% of general population in western countries.[1-4] In India, its prevalence in general population ranges from 9 to 32% in different studies.[5-7]

NAFLD is seen commonly in patients with metabolic abnormalities associated with obesity, such as type II diabetes, dyslipidemia, and metabolic syndrome. Evidently, however, not all obese subjects develop NAFLD and, more importantly, NAFLD can be found in nonobese individuals. Although NAFLD occurring in nonobese subjects has been reported in children and adults of residing in developing countries as well as developed countries. It appears to be recognized more frequently in Asians, even when strict ethnicity specific body mass index criteria are used to define obesity.[8-14] Non-obese NAFLD may represent a distinct entity, rather than merely a by-product of different body mass index (BMI). Moreover, NAFLD in the non-obese subjects suggests a phenotypic distinctiveness that raises the possibility of a different pathophysiology.

NAFLD is assuming higher importance now because of:

1. The possible role in the development of cardiovascular disease;

2. The association with diabetes and impaired glucose tolerance;

3. The strong relationship with metabolic syndrome.

Early diagnosis and management of NAFLD is thus of vital importance.[15]

Recent multinational investigation reveals an increased mortality in non-obese individuals with NASH and NAFLD. Many aspects of lean NAFLD need further exploration including epidemiology

Ultrasound detects fatty liver with a good sensitivity but does not differentiate simple steatosis from steatohepatitis. Serum transaminases have low value in predicting steatohepatitis. The only gold standard test for detection of this fraction with increased risk of progression is liver biopsy. However, application of liver biopsy to all patients with NAFLD is impractical. Various studies have proved that fibroscan has high accuracy in detecting level of fibrosis in NAFLD and can be a good alternative for liver biopsy in patients who cannot undergo invasive procedures. Fibroscan is an easy and non invasive method to evaluate liver fibrosis, needing short time to obtain results.[16]

There is limited information regarding prevalence of fibrosis in non-obese individuals of NAFLD using fibroscan in India.

The objectives of the present study is to estimate the frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

6.2 REVIEW OF LITERATURE

Nonalcoholic fatty liver disease (NAFLD) is a common clinicopathological condition characterized by significant lipid deposition in the hepatocytes of the liver parenchyma. The pathological picture bears a striking resemblance to that of alcohol-induced liver injury, but it occurs in individuals who deny a significant history of alcohol ingestion. NAFLD comprises a wide spectrum of liver damage, ranging from simple macrovesicular steatosis to steatohepatitis, advanced fibrosis, and cirrhosis[17] Subsets of NAFLD which progress to cirrhosis are being increasingly recognized as a major cause of liver-related morbidity and mortality with the potential to progress to liver failure. Before diagnostic tests for hepatitis C were available, cases of NAFLD were diagnosed wrongly as non-A, non-B hepatitis. After advent of tests for hepatitis C and E are available, NAFLD is more accurately defined. The term NAFLD is used to describe a wide spectrum of fatty liver changes ranging from fatty liver and steatosis on one side, to non-alcoholic steatohepatitis (NASH) and cirrhosis on the other.[18]

Definition of NAFLD

NAFLD is deposition of fat in the liver of a non-alcoholic subject, a condition which may progress to end-stage liver disease.

Epidemiology of NAFLD

NAFLD has been reported worldwide but geographic variations in prevalence are evident. Although the worldwide prevalence has not yet been determined, NAFLD is highly prevalent in all continents, but the highest rates being reported from South America (31%) and less common in Africa (14%), prevalence in Asia is reported to be 27%. In India prevalence has been

reported to 30.7%.[20] NAFLD affects all racial and ethnic groups and has no age or sex predilection.

NAFLD is the cause of asymptomatic elevation of aminotransferases in 42–90% of cases once other causes of liver disease are excluded.

Globally, the reported prevalence of nonobese NAFLD varies widely, ranging from 3% to 30%. The prevalence data on nonobese NAFLD between the East and West are not directly comparable at least in part because of the different body mass index (BMI) cut-off values for Asians. The prevalence of nonobese NAFLD described in the literature is summarized in Table 1

Table 1. Prevalence of Nonobese NAFLD [21]

Study	Population	N	Detection	BMI cut-off value, kg/m	Nonobese NAFLD
Fan et al, 2005	China, population-based	3175	US	<23	3.3
Das et al, 2010	India, community-based	1911	US,LB	<23	6.9
Sinn et al, 2012	Korea, community-based (nonobese, nondiabetic)	5878	US	<23	27.4
Omagari et al, 2002	Japan, community-based (nonobese, nondiabetic)	3432	US	<25	12.5
Kim et al, 2004	Korea, community-based (nonobese, nondiabetic)	768	US	<25	16.1
Chen et al, 2006	Taiwan, population-based	3245	US	<25	4.2
Park et al, 2006	Korea, community-based	6648	US	<25	9.8
Dassanayake et al, 2009	Sri Lanka, population-based	2985	US	<25	16.7
Fu et al, 2009	Taiwan, community-based	220	US	<85th	16.0

	(adolescents)			percentile	
Kwon et al, 2012	Korea, community-based	29994	US	<25	12.6
Xu et al, 2013	China, community-based	6905	US	<25	7.3
Lankarani et al, 2013	Iran, population-based	819	US	<25	9.2
Wei et al, 2015	Hong Kong, community-based	911	MRS	<25	19.3

DIAGNOSIS

Symptoms as with many other types of chronic liver disease, most patients with NAFLD (48–100%) are asymptomatic. The liver disease is often discovered incidentally during routine laboratory examination when a hepatic panel reveals an elevated ALT level. When symptoms occur they are usually nonspecific. Vague right upper quadrant abdominal pain, fatigue, and malaise are the most common of these nondescript symptoms. Jaundice, abdominal distension (ascites), gastrointestinal bleeding, and confusion (encephalopathy) are all indicative of advanced liver disease (decompensated cirrhosis), occurring late in the course.[22]

Table 2: Step wise approach to diagnosis of NAFLD

	FINDINGS	FOLLOW UP ACTION
1	Identification of NAFLD and/or NASH	Rule out alcoholism
2	Raised ALT in high risk groups	History from patient relatives
3	Fatty liver on USG or imaging	Random blood alcohol level
4	Exclude other causes like viral, autoimmune, metabolic, etc.	MCV for B12 and/or folic acid deficiency.
5	Liver biopsy (required for diagnostic documentation	AST/ALT ratio, mitochondrial AST/total AST ratio

Biochemical parameters.

Lab parameter

4-5 fold increase in ALT and AST levels, ALT/AST ratio alterations (ALT/AST ratio usually< 1 in cirrhosis, < 2 in alcoholic liver disease). 2-3 fold increase in alkaline phosphatase. GGT is usually normal, upto 2 -3 fold rise in some cases. Bilirubin increases in late stages of NAFLD, albumin decreases in late stages of NAFLD. Prothrombin time increases in late stages of NAFLD S.ferritin raised in upto 50% cases, S. iron is raised and transferrin saturation decreases. Lipids raised in underlying hyperlipidaemia. Viral markers to exclude viral hepatitis

Diagnosis of NAFLD by imaging:

Non-invasive radiological imaging studies such as USG, CT scan of abdomen, and MRI may help in diagnosis of fatty infiltration of liver; but they do not distinguish between fatty liver, steatohepatitis and steatohepatitis with fibrosis – for which liver biopsy is required.

USG examination is to be performed first as it is the least expensive and carries no risk of radiation. Its sensitivity is more, but it lacks specificity.

FIBROSCAN

Non-invasive valuable procedure in the diagnosis of liver stiffness/fibrosis. Application of fibroscan can examine liver stiffness. Diagnosis of liver stiffness and fibrosis by this method has been reported previously. FibroScan was first described in France and then in other parts of the world.[24]

1. In recent years, substantial attention has been focused on one dimensional transient elastography (TE). TE is a non-invasive ultrasound-based method that uses shear wave velocity to assess tissue (*e.g.*, liver) stiffness. The

method was designed at the Langevin institute in 1995 and was initially implemented for quality control in the food industry; however, since 2001, it has been applied in medical practice under the name FibroScan[25]

2. Among the non-invasive tests, transient elastography (FibroScan, TE) with controlled attenuation parameter (CAP) has demonstrated good accuracy in quantifying the levels of liver steatosis and fibrosis in patients with NAFLD, the factors associated with the diagnosis and NAFLD progression.The initial inability of the procedure to accurately determine fibrosis and steatosis in obese patients has been addressed with the development of the obese-specific XL probe. TE with CAP is a viable alternative to ultrasonography, both as an initial assessment and during follow-up of patients with NAFLD. TE assessment of liver fibrosis has predominantly been implemented in patients with chronic viral hepatitis, as well as patients with other chronic liver diseases of different etiologies. Recent studies have examined the usefulness of LSM compared with liver biopsy to identify fibrosis in NAFLD patients.

6.3 AIMS AND OBJECTIVES OF THE STUDY

To determine frequency of fibrosis by fibroscan in non obese individuals of NAFLD.

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

Patients attending the Out Patient Department (OPD) and also admitted in gastroenterology ward of Dayanand Medical College and Hospital, Ludhiana

7.2 METHOD OF COLLECTION OF DATA

Non-obese OPD and IPD patients more than 18 years of age screened using USG for NAFLD were enrolled in this study.

INCLUSION CRITERIA FOR PATIENTS

- Patients with fatty liver diagnosed on basis of USG
- Patients more than 18 years of age with BMI <22.9 KG/M^2 as per asian cutoff for defining obesity.

EXCLUSION CRITERIA FOR PATIENTS

- Age</=18 years
- Body Mass Index (BMI)≥22.9 kg/m2
- Hepatitis B, Hepatitis C or HIV positive
- Consuming more than 20 grams per day of alcohol
- Taking medication containing corticosteroids, estrogen, tamoxifen, amiodarone, antiretroviral medication, cannabis abuse.
- History of IV drug abuse.
- Extra hepatic cholestasis (based on ultrasound or total bilirubin ≥ 2).
- Evidence of liver SOL on ultrasonography.
- Ascites on ultrasonography.
- Pregnancy
- Congestive cardiac failure

- CHRONIC RENAL FAILURE
- STROKE
- ISCHEMIC HEART DISEASE

METHOD

All the patients falling in the sampling frame will be invited to participate in the study. Only those providing informed consent will be included in the assessment.

Non obese NAFLD patients were defined as those having BMI<22.9 kg/m^2 as per asian cutoffs for defining obesity and metabolic syndrome.

Demographic details (age, sex) will be obtained. Personal history related with exposure to risk factors (alcohol, smoking, etc.) were noted, medication history was enquired. Anthropometric measurements were performed and body mass index was calculated. A systemic examination (CVS, Respiratory, Per-abdomen and CNS) was performed.

Blood pressure measurements were done. Hypertension was defined according to NCEP-ATPIII criteria with hypertension defined as BP ≥130/85mmHg and also patients who were actively taking antihypertensive medications. A 2 ml blood sample of the patients was collected under aseptic conditions. The following hematological and biochemical assessments were performed:

1. Hemoglobin
2. Hematocrit
3. Fasting glucose
4. Fasting insulin
5. S. Lipid Profile (Total Cholesterol, Triglyceride, HDL-c, LDL-c)

6. S. Bilirubin (Total)

7. S. Bilirubin (Direct)

8. S. Alkaline Phosphatase

9. S. AST

10. S. ALT

11. S. Total Protein

12. S. Albumin

13. S. Urea

14. S. Creatinine

15. S. Sodium

16. S. Potassium

17. Thyroid stimulating hormone (TSH)

- All blood investigations needed for this study were performed in biochemistry, pathology and microbiology labs in DMCH. All the patients underwent electrocardiographic assessment; Viral Markers (HBV, HBsAg, HIV) were assessed by ELISA. Chest X-ray PA view was performed. Fatty liver was defined on the basis of USG abdomen (hyperechoic liver where the echo-texture of the liver was brighter than the kidney, and had blurred vascular margins and deep attenuation of ultrasound signal) and was done by a single observer in Deptt. of Radiology, DMCH. Ultrasound gradings of fatty liver was graded as: Grade I: echogenicity is just increased Grade II: when the echogenic liver obscures the echogenic walls of portal vein branches Grade III: echogenic liver obscures the diaphragmatic outline Fibroscan was done in Deptt. Of Gastroenterology, DMCH (endoscopy complex) by a single observer on Echosens machine who measured liver

fibrosis and liver steatosis. Grading of fibrosis was done: F0-F1 – 0-6 kpa F2 - 6.1 - 8kpa F3 – 8.1-10kpa F4 - ≥10kpa.

SAMPLE SIZE

All non obese NAFLD patients attending the OPD and admitted in gastroenterology department of DMCH within 1 year (March, 18 to march, 19) will be enrolled in this study

OUTCOME

PRIMARY OUTCOME:

To determine frequency of fibrosis by fibroscan in non-obese individuals of NAFLD.

SECONDARY OUTCOME:

Correlation of fibrosis in non-obese individuals of NAFLD with age, diabetes and hypertriglyceridemia.

STATISTICAL ANALYSIS

Presence and absence of fibrosis and its grading in non-obese individuals with NAFLD will be analysed using Chi-square test. SPSS software shall be used for statistical analysis.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes, the study requires investigations.

Tests include

Hemoglobin

2. Hematocrit

3. Fasting glucose

4. Fasting insulin

5. S. Lipid Profile (Total Cholesterol, Triglyceride, HDL-c, LDL-c)

6. S. Bilirubin (Total)

7. S. Bilirubin (Direct)

8. S. Alkaline Phosphatase

9. S. AST

10. S. ALT

11. S. Total Protein

12. S. Albumin

13. S. Urea

14. S. Creatinine

15. S. Sodium

16. S. Potassium

17. Thyroid stimulating hormone (TSH)

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes attached herewith.

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PROFORMA

Sr. No. ___

Name MRD No.

Age/Sex DOA

Occupation DOD

Address

PRESSENTING COMPLAINTS

PAST HISTORY:

Diabetes mellitus

Hypertension

Bronchial asthma

Coronary Artery Disease

Koch's

FAMILY HISTORY:

PERSONAL HISTORY

- Alcohol
- Smoking
- Other substances abuse

Signature of Candidate **Signature of Supervisor**

- Desi medications
- Menstrual history(in case of female patients)

TREATMENT HISTORY

GENERAL PHYSICAL EXAMINATION

Pallor: Y/N	Icterus: Y/N	Pedal edema: Y/N
Pulse rate	B.P	Temp.
R.R	Weight	waist/hip ratio
Height	BMI	

SYSTEMIC EXAMINATION

CVS

CHEST

P/A

CNS

Signature of Candidate **Signature of Supervisor**

INVESTIGATIONS

Hemoglobin	
Bilirubin (T)	
Bilirubin (D)	
ALP	
AST	
ALT	
Total proteins	
Albumin	
Urea	
Creatinine	
Sodium	
Potassium	
TSH	
FBS	
Lipid profile	
Fasting Plasma Insulin	
HBA1C	
Urine r/e	
ECG	
Anti HCV (by ELISA)	
HBsAG (by ELISA)	
HIV	
X-ray chest PA view	

FIBROSCAN

ULTRASOUND

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... am willing to participate in the study **"TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out of the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____ निवासी _____ इस शोधकार्य "**TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"TO STUDY FREQUENCY OF FIBROSIS IN NON-OBESE INDIVIDUALS OF NAFLD" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ